EVIDENCE OF FUNCTIONAL REMODELLING OF THE RIGHT AND LEFT VENTRICLE IN ATHLETES

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Abstract

BACKGROUND: Cardiac remodelling following athletic training manifests as changes in structure and function. Dichotomous remodelling of the left ventricle (LV) in response to strength and endurance training has been suggested by cross-sectional design, purportedly owing to the divergent haemodynamic 'pressure' load elicited by static, resistance training and haemodynamic 'volume' load caused by dynamic, endurance training. Compared with the LV, the right ventricle (RV) is more sensitive to the acute haemodynamic response, and long-term remodelling of endurance training, which elicits both a volume and pressure load on the RV. The purpose of this thesis was to further the understanding of cardiac adaptation and functional cardiac responses in the athlete's heart.

METHODS: Meta analyses (*Study 1*) were performed on RV systolic pressures, at rest and during exercise, and measures of RV function at rest including displacement, velocity and regional longitudinal strain, comparing the weighted mean difference between high-dynamic athletes and non-athletic controls. Using echocardiography, experimental *Study 2* examined the RV free wall response to acute plasma volume expansion, achieved via 7 ml·kg^{-1} intravenous Gelofusine infusion, and subsequent leg raise in endurance-trained (*n* = 13) and non-trained controls (*n* = 11). In experimental S*tudy 3* echocardiography was used to compare the LV responses of endurance-trained (*n* = 15), resistance trained (*n* = 14) and non-athletic men (*n* = 13) to (i) progressive isometric leg-press exercise (i.e., pressure load; 20, 40, 60% one-repetition maximum) and (ii) an intravenous Gelofusine infusion (7 ml·kg^{-1}) with and without passive leg-raise (i.e., progressive volume load).

RESULTS: Via meta-analysis (*Study 1*), it was established that right ventricular systolic pressure was significantly greater in endurance athletes at rest (2.9 mmHg, $P = 0.0005$) and during exercise (11.0 mmHg, $P < 0.0001$). Resting RV myocardial displacement (1.8 mm, $P < 0.0001$) and tissue velocity (0.7 cm/s, $P = 0.001$) were also greater in endurance athletes.

RV free wall longitudinal strain was similar compared with controls, but apical strain was greater (0.9%, $P = 0.03$) and basal strain lower (-2.5%, $P < 0.0001$), in endurance athletes, demonstrating a regional adaptation. *Study 2* examined the RV free wall response to acute plasma volume expansion. Both endurance-trained individuals ($7 \pm 3\%$) and controls ($7 \pm 3\%$) experienced an increase in free wall strain, which was also similar following leg raise ($4 \pm 3\%$ and $7 \pm 3\%$, respectively; $P = 0.793$). However, infusion evoked a greater increase in basal longitudinal strain in endurance-trained vs. controls ($18 \pm 4\%$ vs. 5 ± 5; $P = 0.074$), which persisted following leg raise ($18 \pm 3\%$ vs. $1 \pm 5\%$; $P = 0.041$). In S*tudy 3* resistance-trained participants preserved stroke volume ($-3 \pm 8\%$) versus non-athletic controls at 60% 1 repetition maximum ($-15 \pm 7\%$, $P = 0.001$). Time-to-peak longitudinal LV strain was maintained in resistance-trained individuals and delayed in endurance-trained participants (1 vs 12% delay, $P = 0.021$). Volume infusion caused a similar increase in end-diastolic volume and stroke volume across groups, but leg raise further increased end-diastolic volume only in endurance-trained individuals ($5 \pm 5\%$ to 8 ± 5, $P = 0.018$).

CONCLUSIONS: Collectively, this thesis highlights the remodelling capacity of the male athlete's heart, which extends beyond simply the expression of structural or functional remodelling at rest, and incorporates a training-specific, adaptive response associated with the attendant haemodynamic perturbation.

To my family, you have provided me the platform that has enabled me the freedom to achieve my goals. Your patience, understanding and generosity are so valued. Whilst I agree that luck may be merely the combination of opportunity and preparation, you have ensured that I be exposed to bountiful opportunity and for that I am eternally grateful.

Lastly, and most importantly, to Bry, no one is more thankworthy than you. Your unwavering support over the last few years is far more than I could have asked for. Without your tremendous understanding and encouragement in the lab and at home, it would have been impossible to complete this thesis.

Let our adventure continue.

"Pressure makes diamonds, but it can also create volcanoes."

Rob Shave & Mike Stembridge

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List of key cardiac terminology with accompanying abbreviations and definitions

Term	Abbreviation	Definition
Preload	-	Ventricular wall stress or tension at the end of diastole
Afterload	-	Ventricular wall stress or tension during systole
Inotropy	-	Intrinsic contractile property of cardiac myofibres
Chronotropy	-	Rate of ventricular contraction
Systole	-	Contraction phase within the cardiac cycle from mitral valve closure to aortic valve closure
Diastole	-	Relaxation phase within the cardiac cycle from aortic valve closure to mitral valve closure
Ejection Fraction	EF	The amount of blood ejected with each contraction, expressed as a percentage of end-diastolic volume
Left Ventricular End-Diastolic Volume	LV EDV	The volume of blood within the left ventricle at the end of diastole
Left Ventricular End-Systolic Volume	LV ESV	The volume of blood within the left ventricle at the end of systole
Stroke volume	SV	The volume of blood ejected by the ventricle with each contraction.
Fractional Area Change	FAC	Difference in RV EDA and RV ESA, divided by RV EDA
Right Ventricular End-Diastolic Area	RV EDA	The area within the right ventricle at the end of diastole, measured from an RV focused 4 chamber view
Right Ventricular End-Systolic Area	RV ESA	The area within the right ventricle at the end of systole, measured from an RV focused 4 chamber view
Pulmonary Artery Systolic Pressure	PASP	The peak pressure within the pulmonary artery during systole
Right Ventricular Systolic Pressure	RVSP	The peak pressure within the right ventricle during systole
Tricuspid Annular Systolic Excursion	TAPSE	The excursion of longitudinal displacement of the tricuspid annulus during systole
Early Ventricular Filling Velocity	E	The peak velocity of blood flow from atria to ventricle in the early phase of diastole
Late Ventricular Filling Velocity	A	The peak velocity of blood flow from atria to ventricle in the late phase of diastole, corresponding with atrial contraction
Strain	-	The percentage of deformation of the myocardium from diastole to systole

Chapter 1

General Introduction

Chapter 1. General Introduction

1.1 Background to Thesis

The athlete's heart has been a topic of great interest and intrigue to sports cardiologists and physiologist alike over the last century. Initial reports of cardiac enlargement and sinus bradycardia date back to the late 1800's and early 1900's (Henschen, 1899; Darling, 1899). The adaptive remodelling of the athlete's heart is clinically important, given the phenotypic resemblence to cardiomyopathy (Maron, 2005; Baggish & Wood, 2011; Galderisi *et al.*, 2015). The term 'grey zone' has been coined to reflect this diagnostic uncertainty (Maron, 2003). As such, there has been considerable effort from the clinical and scientific community to define what is 'normal' cardiac structure in athletes.

The cardiac structural phenotype reported in different types of athletes was initially characterised by the seminal 'athlete's heart' study by Morganroth and colleagues (Morganroth *et al.*, 1975), which reported dichotomous structural remodelling of the left ventricle (LV) between endurance and resistance-trained athletes. The authors hypothesised that training-specific remodelling was associated with the differential haemodynamic loading, whereby endurance athletes experienced eccentric remodelling (i.e., a balanced increase in LV mass and LV cavity dimension), due to volume overload and increased diastolic wall stretch (i.e., preload); endurance sports (dynamic exercise such as running, swimming rowing and cycling) are predominantly aerobic activities, requiring elevated cardiac output over a long period of time with marked increase in oxygen consumption and normal or reduced peripheral vascular resistance (Mitchell *et al.*, 1994). In contrast, it was hypothesised that resistance training resulted in concentric remodelling (i.e., an increased LV wall thickness without a change in cavity size) which was proposed to be due to a pressure overload and increased LV systolic wall stress (i.e., afterload). Resistance training (e.g. weightlifting, wrestling, etc.) requires muscular contraction to build the strength, anaerobic endurance and/or size of skeletal muscles, and generates only

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a small increase in oxygen consumption and cardiac output, but a substantial increase in blood pressure (Mitchell *et al.*, 1994). As such, the haemodynamic load on the heart greatly differs according to the type of exercise performed. In addition to structural changes, subsequent assessment of LV function also suggests a divergent functional adaptation to resistance or endurance exercise; enhanced diastolic function may compensate for a lower baseline systolic function in endurance-athletes (Baggish *et al.*, 2008*a*; Beaumont *et al.*, 2017*a*), whilst in resistance athletes an improved systolic function (Beaumont *et al.*, 2017*a*) may offset a reduction in diastolic function (Baggish *et al.*, 2008*a*).

The right ventricle (RV) was omitted from the initial observations of Morganroth et al. (1975). In regards to resistance exercise, the RV is unlikely to be significantly challenged, since pulmonary vascular resistance is not directly influenced in the same way in which systemic vascular resistance is perturbed. In contrast, RV end-systolic wall stress increases greatly during peak cycling exercise (La Gerche *et al.*, 2011). Furthermore, structural remodelling is pronounced in endurance athletes (La Gerche *et al.*, 2017), often meeting clinical task-force criteria for arrhythmogenic cardiomyopathy (Prior & La Gerche, 2020) and displaying region-specific adaptations including preferential dilation at the base (La Gerche *et al.*, 2011; D'Andrea *et al.*, 2013) and hypertrabeculation at the apex (D'Ascenzi *et al.*, 2017*a*). An understanding of normal RV function in endurance athletes, therefore, is of great importance to sports cardiologists. In the same way that structural remodelling differs across different regions of the RV, functional adaptation across the myocardium may also be region-specific (Teske *et al.*, 2009). A plethora of studies reporting RV function containing small samples of athletes have been published within the last decade, although normal reference values for RV function at rest are not yet established. Nonetheless, characterisation of resting right and left ventricular function may be of limited use, because a lower baseline function may simply reflect an enhanced functional reserve capacity (Nottin *et al.*, 2008; La Gerche *et al.*, 2012*a*; Lakatos *et al.*, 2020). Arguably more

important, although comparably less extensively investigated, is the *functional response* when the heart is stressed. Furthermore, in extension to the stimulus-specific structural remodelling proposed by Morganroth et al. (1975), the myocardial functional response to specific haemodynamic stress may depend on the attendant haemodynamic load. If such stimulus-specific functional remodelling exists, it is possible that this divergent adaptation occurs at the expense of a trade-off in the endurance-and resistance-athlete's heart to accommodate pressure and volume, respectively.

The aim of this thesis was to further the understanding of cardiac adaptation and functional cardiac responses in the athlete's heart. Accordingly, one meta-analysis and two experimental studies were completed at Cardiff Metropolitan University between April 2016 and February 2020. The next chapter in this thesis provides an overview of existing literature pertinent to the athlete's heart. The third chapter outlines the general methodology used in the experimental studies. In Chapter 4, a meta-analysis was conducted to examine and compare RV function in endurance athletes in comparison to non-athletic controls. Subsequently, the functional RV response to an increase in circulating volume (achieved via intravenous volume infusion and passive leg-raise) is provided in Chapter 5, with specific comparison of endurance athletes vs. non-athletic controls. In Chapter 6, the functional LV response of endurance and resistance-trained athletes and non-athletic controls were compared following both an increase in circulating volume (i.e., volume load) and during isometric leg-press exercise designed to increase arterial blood pressure (i.e., pressure load). Finally, the overall findings are discussed, and key conclusions of the thesis are presented in Chapter 7. Data from these chapters have been published in two world leading physiology journals (**Appendix VIII**) and multiple conferences (**Appendix I**).

Chapter 2

Review of Literature

Chapter 2. Review of Literature

2.1 Introduction

The heart of athlete's has been a topic of great scientific interest for over a century. Cardiac enlargement in athletes, for example, was first reported in the late 1880's (Henschen, 1899; Darling, 1899). In the mid 1970's, Morganroth and colleagues (1975) proposed a dichotomous structural remodelling pattern of the LV associated with resistance- or endurance-training, due to the attendant haemodynamic pressure or volume stimulus, respectively. Numerous researchers since then have helped to establish normal features of the endurance athlete's heart, including electrical, functional and structural cardiac adaptations (Vinereanu *et al.*, 2001; Maron, 2005; Oxborough *et al.*, 2012*b*; Sharma *et al.*, 2017; Lord *et al.*, 2018). However, many studies assessing structure and systolic function have done so while the athlete is resting. Relatively few investigations have compared training-specific adaptations during states of increased haemodynamic load, and it is plausible that the functional *response* in this context is specific to the repetitive haemodynamic stimulus to which the ventricle is repeatedly exposed to during exercise.

The focus of this literature review is aimed at providing an overview of normal left and right ventricular function, followed by the haemodynamic response to both resistance and endurance exercise, and the associated structural remodelling. Finally, the literature pertinent to functional adaptation of the LV and RV is evaluated, and the aims and hypotheses of this thesis are presented.

2.2 Normal Cardiac Structure and Function

2.2.1 Left Ventricular Anatomy and Function

Normal LV geometry has been conceptualised as a prolate ellipsoid shape (similar to that of a bullet; **Figure 1**) (Rankin *et al.*, 1976), with a long axis from apex to base. Short axis

cross-sections of the LV have revealed a rough circular geometry that is skewed by both a flat anterior wall and a curved posterolateral wall, as well as an irregular endocardial surface due to the presence of papillary muscles and trabeculae (Rankin *et al.*, 1976). Global cardiac function is commonly determined by ejection fraction (EF), which reflects the percentage of blood ejected relative to the volume of blood at end-diastole. However, this simple surrogate of cardiac function oversimplifies the complexity of the LV, and provides no information about myocardial contraction or relaxation.
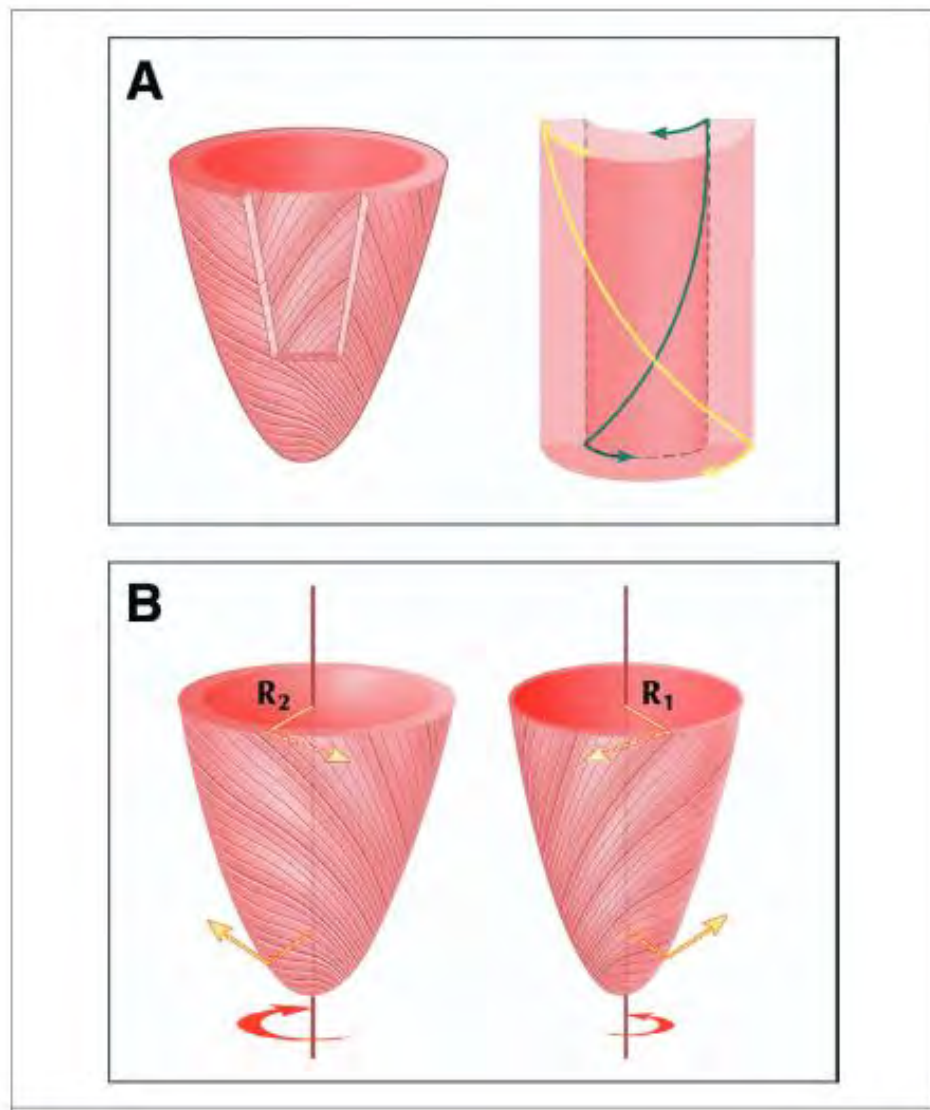
Figure 1. LV geometry and architecture.

Myofibre orientation in the LV changes from a left-handed helix in the subepicardium to a right-handed helix in the subendocardium (A, left). Simultaneous contraction of both helical layers results in a longitudinal deformation.

Within the LV myocardial wall, myofibre geometry changes from a right-handed helix in the subendocardium to a left-handed helix in the subepicardium (Taber *et al.*, 1996). The direction of rotation favours the outer epicardial layer due to the mechanical advantage of a larger radius of rotation (Taber *et al.*, 1996; Sengupta *et al.*, 2006), resulting in a counterclockwise rotation at the apex and a clockwise rotation at the base. The LV base is pulled towards the apex, shortening in the longitudinal axis, whilst the apex remains relatively stationary. During myocardial contraction, therefore, the LV wall shortens, thickens, and twists. The LV untwisting is a key component of diastolic function, generating an intraventricular pressure gradient and thereby contributing to the 'suction' of blood into the ventricle. Myocardial shortening can be quantified, non-invasively, by measuring regional strain (i.e., deformation). Myocardial strain represents the percentage change in myocardial length from its initial state which reflects the shortening or thickening of the myocardium (Johnson *et al.*, 2019). Further detail of how this can be quantified is provided in Chapter 3.6.4. Contraction in the longitudinal plane is also reflected by a rapid movement of the myocardium during systole (S') and early (E') and late diastole (A'). Blood flow through the mitral annulus during diastole also reflects diastolic filling, whereby the velocity of early filling (E) should be greater than that provided during late diastole (A) via atrial contraction (Armstrong *et al.*, 2010).

2.2.2 Right Ventricular Anatomy and Function

The RV is responsible for pumping blood through the pulmonary circulation. Unlike the ellipsoid shape of the LV, the RV is approximately triangular in the longitudinal plane and crescent-shaped in the cross-sectional plane, as it wraps around the LV (Ho & Nihoyannopoulos, 2006). The shape of the RV is also influenced by the interventricular septum, which is concave and bulges towards the RV, predominantly due to the transseptal pressure gradient (Ho & Nihoyannopoulos, 2006). In normal conditions, RV volume is greater than that of the LV, despite a substantially lower RV mass (approximately one sixth

of the LV) (Lorenz *et al.*, 1999). The RV chamber can be described as three components according to Goor and Lillehei (Goor & Lillehei, 1975): i) the inlet, which consists of the tricuspid valve, chorea tendineae and papillary muscles, ii) the trabeculated apex, and iii) the smooth myocardial outflow tract, extending to the pulmonary valve (**Figure 2**). The RV can also be divided into basal, mid, and apical sections (Ho & Nihoyannopoulos, 2006).
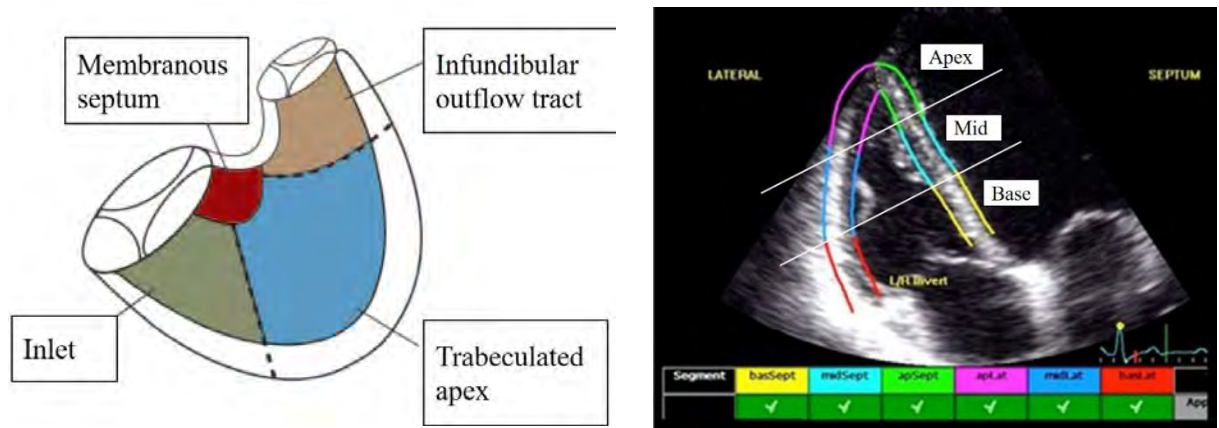
Figure 2. Anatomy of the RV.

RV composed of the three segments including i) the inlet, the trabeculated apex and the smooth myocardial outflow tract (left) amended from (Haddad *et al.*, 2008) and the RV divided into the i) basal, ii) mid-level and apical sections on a typical apical four chamber echocardiogram.

The normal RV wall is thin (3-5 mm) and comprised of a superficial myofiber layer and a deep layer. The fibres of the superficial layer are arranged predominantly circumferentially, causing an inward motion of the free wall. These fibres turn obliquely toward the apex, continuing to form the superficial fibres of the LV and spiralling to form the deep myofibers (**Figure 3**) (Ho & Nihoyannopoulos, 2006). In contrast, the deep layer is aligned longitudinally from base to apex, and contributes to both longitudinal shortening and tricuspid annular displacement towards the apex during contraction (Haddad *et al.*, 2008). The interventricular septum is formed by oblique cross-striated helical bands which

also contribute substantially to longitudinal motion (Buckberg & Hoffman, 2014). In healthy individuals, under normal loading conditions, circumferential fibre constriction of the RV causes a minor bellows effect (inward motion of RV free wall). Most of the RV systolic ejection, however, can be ascribed to longitudinal shortening (Ho & Nihoyannopoulos, 2006; Haddad *et al.*, 2008), including the coiling of the helical bands of the septum (Buckberg & Hoffman, 2014). Nearly 80% of RV systolic ejection is associated with longitudinal shortening by atrioventricular plane displacement, compared to approximately 60% within the LV (Carlsson *et al.*, 2007; Brown *et al.*, 2011).
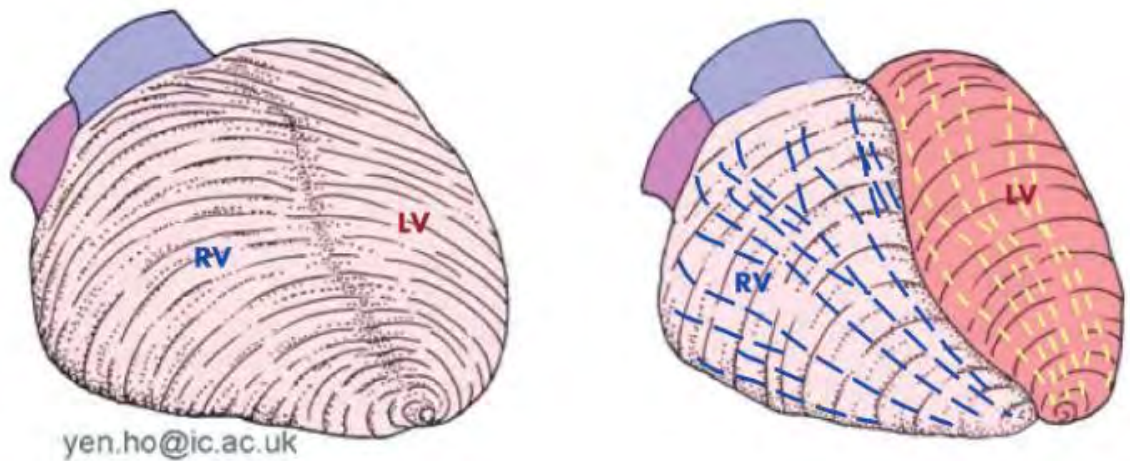
Figure 3. **A simplistic model of the myofiber orientation of the RV**.

Demonstrating the circumferential to oblique arrangement of the myofibres in the epicardium which spiral to form the superficial fibres of the LV at the apex (left) and the deeper layer of myofibres oriented longitudinally from base to apex. Taken from Ho & Nihoyannopoulos (2006).

2.2.3 Contraction (The Cardiac Myocyte)

The contractile force of the myocardium is generated by cardiac myocytes. The myofibrils of these cells are organised into sarcomeres, which consist of myosin-containing thick filaments and actin-containing thin filaments that form the basic contractile unit within the myocyte (Levick, 2010). As the myocardium contracts and relaxes, the thick and thin

filaments slide past one another and create cross-bridges. This process enables the sarcomere length to shorten and the myocyte to contract, which forms the basis for the sliding filament theory of muscle contraction (Levick, 2010). The contraction of the cardiac myocyte is dependent upon changes in intracellular calcium concentration (Eisner *et al.*, 2017). Normal contraction requires that calcium be sufficiently high during systole and low during diastole. During systole, calcium binds to troponin C, exposing the myosin binding sites on the actin molecule and enabling cross-bridges to be formed. The energy for crossbridge cycling is provided by adenosine triphosphate (ATP) which is broken down during the process. Upon completion of systole, calcium ions dissociate from their binding sites, and calcium is returned to the sarcoplasmic reticulum. The decline in cytosolic calcium concentration separates the cross-bridges, ending contraction, and the myofibrils return to their inactivated position (Levick, 2010).

2.2.4 Contractility, Preload and Afterload

Contractility, or inotropic state, is defined as the ability of the myocardium to contract (Klabunde, 2012). The inotropic state of the heart is primarily governed by the autonomic nervous system (ANS), which is divided into the sympathetic and parasympathetic nervous systems. The parasympathetic system is most active under restful conditions, whilst the sympathetic system is more active during stressful conditions. During heightened states of stress, such as during exercise, high levels of epinephrine augment sympathetic adrenergic effects. Increased sympathetic activity activates β1-adrenergic receptors, increasing the cytosolic free calcium transient and thus increases contraction of the ventricle (Gordan *et al.*, 2015).

In addition to autonomic regulation of contractility, cardiac function is regulated by a number of other factors, including preload and afterload. Definitions of preload and afterload can be developed using the law of LaPlace to describe the relationships between chamber pressure, chamber radius and wall thickness (Norton, 2001). In the context of the

law of LaPlace, wall stress (σ) is proportionate to pressure (p) and radius (r), and inversely proportional to wall thickness (h) ($\sigma = \frac{p \times r}{h}$). The term preload can be defined as the ventricular wall stress or tension at the end of diastole, whilst afterload is used to define the wall stress during systole (Norton, 2001). When venous return is increased, for example during dynamic exercise, end-diastolic pressure and volume is increased which causes a greater myocardial stretch and an increase in the sarcomere length-tension relationship (Patterson & Starling, 1914; Allen & Kentish, 1985). The greater actin-myosin overlap achieved with greater myocardial stretch facilitates an increase in the force of contraction, known as the Frank-Starling mechanism. Other mechanisms intrinsic to the myocardium may also alter the inotropic state of the heart. An increase in afterload, due to an increase in arterial pressure during resistance exercise for example, is subsequently followed by an enhancement in contractility, which allows the ventricle to recover towards its normal volume (von Anrep, 1912), i.e., homeometric autoregulation (Sarnoff *et al.*, 1960). Fundamental to the Anrep effect is a progressive increase in the calcium transient amplitude that is initiated by Angiotensin II and endothelin release, activating redox sensitive kinases and intracellular Na+ concentration, resulting in upregulation of the Na+/Ca+ exchanger (Cingolani *et al.*, 2013). In addition to the aforementioned mechanisms, contractility can be enhanced through increases in contraction frequency, otherwise known as the Bowditch effect or frequency-dependent activation (i.e., an increase in contractile function with an increase in heart rate) (Mulieri *et al.*, 1992; Bombardini *et al.*, 2005). The Bowditch effect is attributed to an up-regulation of calcium entry, with a more rapid release and reuptake of calcium from the sarcoplasm (Balcazar *et al.*, 2018). Additionally, an increase in coronary perfusion has been reported to increase LV contractile function (Gregg Phenomenon; (Gregg, 1963). An increase in microvascular volume opens stretch-activated channels and calcium influx in the cardiac muscle cells is increased followed by an increase in calcium sensitivity of the contractile apparatus (Westerhof *et al.*, 2006).

2.2.5 Pressure-Volume Interaction

The interaction between ventricular pressure and volume is fundamental in understanding the cardiac cycle. This is particularly true in the context of exercise, when ventricular load is substantially altered dependent on the ventricle studied and the type of exercise performed. The pressure generated and volume ejected during systole are determined by ventricular performance and the effective arterial afterload (Tedford, 2014; Brener *et al.*, 2020). Using invasive procedures, these parameters can be represented on a pressure-volume loop diagram as end-systolic ventricular elastance (Ees) and arterial elastance (Ea), respectively. RV or LV Ea represents the complex haemodynamics of the pulmonary or systemic vasculature, respectively, calculated as ESP/SV, and reflects the total (lumped) hydraulic load the ventricle ejects against. Ventricular contractility is reflected by the end-systolic pressure-volume relationship (ESPVR; **Figure 4**), which describes the maximal pressure that can be generated by the ventricle at any given volume. As such, the slope of ESPVR (Ees) is acquired by assessing the pressure-volume loops at different preloads. Pressure-volume loops provide insightful and accurate indices of ventricular contractility and compliance, but require invasive procedures that are not averse from risk (Burkhoff *et al.*, 2005). Alternatively, non-invasive assessment of the heart, such as echocardiography and cardiac magnetic resonance imaging (cMRI), are frequently employed and permit the assessment of cardiac structure and myocardial function.
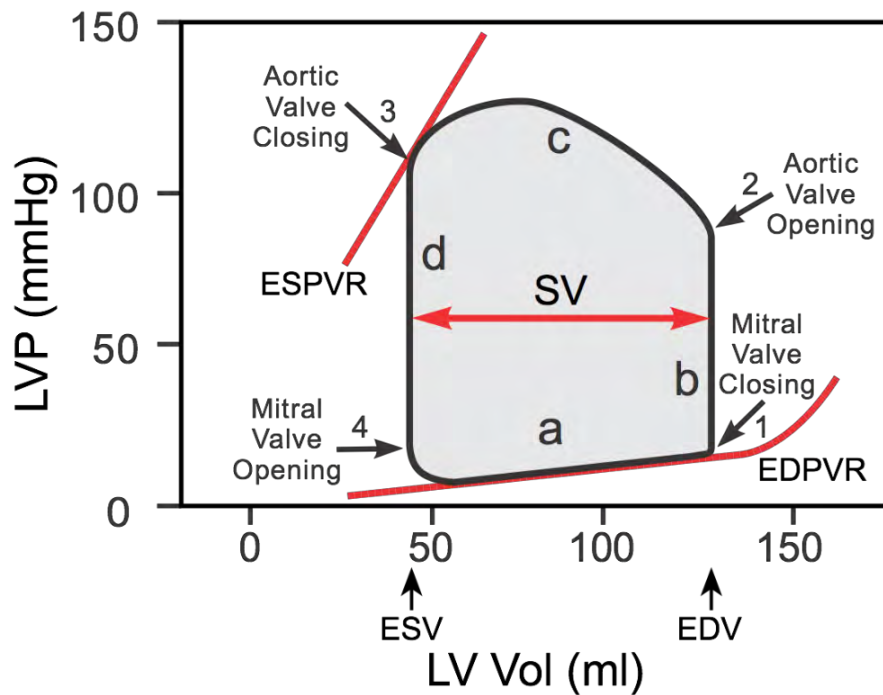
Figure 4. Simplistic LV pressure-volume loop divided into four phases

Taken from Klabunde (2012). Ventricular filling (phase a; diastole), isovolumic contraction or pre-ejection interval (phase b; systole), ejection (phase c; systole) and isovolumic relaxation or post-ejection interval (phase d; systole). Point 1 reflects the pressure and volume within the ventricle at the end of ventricular filling. The mitral valve remains closed as the ventricle begins to contract, causing an increase in ventricular pressure without a change in ventricular volume, i.e., isovolumic contraction (phase b). Once ventricular pressure exceeds downstream aortic pressure, the aortic valve opens (point 2) and ejection (phase c) begins. Ventricular volume decreases throughout ejection as ventricular pressure increases. Closure of the aortic valve signifies the end of LV ejection (point 3), at which point ventricular relaxation follows without a change in volume (i.e., phase d; isovolumic relaxation). When ventricular pressure falls below atrial pressure, the mitral valve opens (point 4) and the ventricle begins to fill (phase a).

2.2.6 Haemodynamic Regulation

Beat-to-beat fluctuations in haemodynamic parameters reflect the presence of physiological stress and the dynamic cardiovascular response to maintain homeostasis. For example, the cyclic variations in intrathoracic pressure with breathing alters venous return, pulmonary and aortic pressures (Bainbridge, 1920), and cyclic changes in heart rate due to the mechanical sensing of stretch receptors (Bainbridge, 1920). The same factors that govern

the flow of fluid is based upon Ohm's law of physics, which states that flow (F) equals the

pressure difference (gradient; ΔP) divided by resistance (R):

$$F = \frac{\Delta P}{R}$$

Arterial and venous pressures are usually maintained within a narrow range, owing

primarily to the autonomic nervous system control of the cardiovascular system. Reflex-

mediated changes in efferent outflow from the cardiovascular control centres regulate blood

pressure and heart rate, in response to afferent stimulation. These reflexes include i) the

arterial baroreflex, ii) arterial chemoreflex, iii) baroreflex from within the heart and

pulmonary vasculature, iv) skeletal muscle mechanoreflex and metaboreflex, and v) central

command. These reflexes act to control blood pressure both at rest and during physiological

stress. During exercise, for example, the baroreflex stimulus-response is reset, allowing the

baroreflex to operate at higher arterial blood pressures evoked by the exercise (Raven *et

al.*, 2006). The pulmonary circulation differs to that of the systemic, in that it is under

minimal resting tone, and is almost fully dilated under normal conditions (Hughes &

Morrell, 2001). As such, as opposed to the LV, the RV ejects blood into a low-pressure,

high-compliance pulmonary circulation.

2.3 Haemodynamic Response to Endurance Exercise

Dynamic exercise poses a substantial challenge to the cardiovascular system, as metabolic

demand requires a significant rise in cardiac output (Lewis *et al.*, 1983), which is the

primary factor limiting maximal oxygen consumption (Saltin, 1985). Within the first few

minutes of submaximal, constant-intensity exercise, cardiac output typically reaches a

steady state, while total peripheral resistance declines (Higginbotham *et al.*, 1986;

Tschakovsky & Hughson, 2003), systolic arterial blood pressure increases and diastolic

blood pressure remains relatively stable (Miyai *et al.*, 2002). Increased sympathetic nerve

activity and a concomitant decline in parasympathetic activity result in an increased heart rate and shortened cardiac cycle, which is predominantly achieved by reducing diastolic filling time (Chung *et al.*, 2004). Enhanced oxygen consumption ($\dot{V}O_2$) during exercise is mediated by an increase in oxygen extraction by metabolically active tissue (Bangsbo, 2000) and an increased blood flow to active muscles. Higher blood flow is achieved by an increase in cardiac output, and a redistribution of blood via vasoconstriction of non-active areas (Tschakovsky 2002). Functional sympatholysis, (i.e., an attenuated sympathetic vasoconstrictor response in active musculature) also ensures that perfusion is matched closely with metabolic demand (Remensnyder *et al.*, 1962; Hansen *et al.*, 1996). A persistent increase in blood flow during exercise creates a shear stress stimuli associated with nitric oxide dependent vascular adaptation (Green *et al.*, 2005), increasing lumen diameter and thereby reducing systemic vascular resistance (Green *et al.*, 2012). Heart rate also increases with increasing exercise load; however, the stroke volume (SV) response to exercise is inconsistent between trained and untrained individuals (Gledhill *et al.*, 1994; Stickland *et al.*, 2006*b*), and will be discussed further in the following subsection (Chapter 2.3.2).

Exercise-induced blood volume expansion (mediated by increased thirst, reduced urinary excretion, and greater total circulating protein), increases central venous pressure (CVP) (Sawka *et al.*, 2000), thereby increasing RV preload and consequently LV preload, increasing LV end-diastolic diameters and LV SV via better utilisation of the Frank-Starling mechanism. Initially, the blood volume expansion is mediated by an increase in plasma volume, with virtually no change in red cell mass (**Figure 5**). With prolonged training (> 2 - 4 weeks in duration), erythropoiesis stimulates an increase in red cell mass, and hence blood volume expansion is more evenly distributed between plasma volume and red cell volume (Sawka *et al.*, 2000).
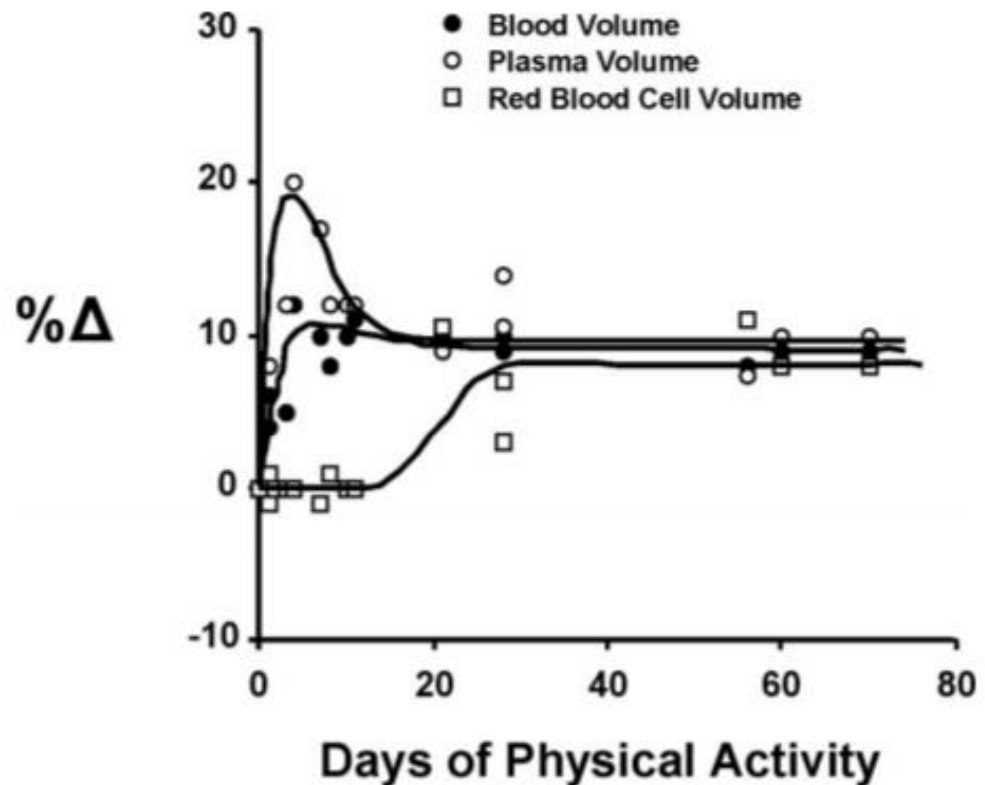
Figure 5. **Estimated time course of relative change (Δ%) in blood volume, plasma volume and erythrocyte volume.**

Blood volume (closed circles), plasma volume (open circles), and erythrocyte volume (open squares) during adaptation to regular physical activity. Taken from Sawka et al. (2000).

Unlike most organs in the mammalian body, the lungs receive almost all of the cardiac output. The already low resistance in the pulmonary vasculature is reduced further when cardiac output is augmented via the distention of perfused vessels and the recruitment of previously unopened vessels (West, 2000), allowing an increase in pulmonary capillary blood volume (Dempsey, 2019). Lewis et al. (2013) observed an increase of 1.5 mmHg in mean pulmonary artery pressure for each 1 litre increase in cardiac output. Thus, an increase in cardiac output of 30 L/min, similar to that achieved during exercise, would equate to a mean pulmonary artery pressure of greater than 50 mmHg, representing a threefold increase

from rest. Substantial elevations in pulmonary artery pressure have a significant impact upon RV afterload, discussed further in Chapter 2.3.2.

2.3.1 Left Ventricular Response to Endurance Exercise in a Normal Heart

SV is influenced by venous return, ventricular distensibility, diastolic filling, and the force of contraction in relation to arterial pressure (Åstrand *et al.*, 2003). During exercise, heart rate increases, and LV filling time decreases from ~0.55 s at 70 bpm to ~0.12 s at 195 bpm (George *et al.*, 2010). Despite this reduced diastolic filling time, in healthy individuals, increased venous return to the heart is facilitated by the skeletal muscle (Laughlin, 1987) and respiratory pump systems (Miller *et al.*, 2005), causing an increase in end-diastolic volume (EDV) (Sundstedt *et al.*, 2004). Diastolic function, assessed by Doppler interrogation of blood filling velocities (E wave) and tissue velocities (E'), increase progressively with exercise intensity (D'Andrea *et al.*, 2001; Stoylen *et al.*, 2003). Indeed, the increase in SV at exercise onset appears to be mainly related to early diastolic filling (E wave) (Izem *et al.*, 2019). Torsion, twisting, and untwisting velocities are increased (Tischler & Niggel, 2003; Notomi *et al.*, 2006; Beaumont *et al.*, 2017a). Untwisting velocity may contribute to the generation intraventricular pressure gradients, creating a suction that augments LV filling during exercise (Notomi *et al.*, 2006). The rapid reduction in LV pressure allows the LV to fill at low left atrial pressures. Interestingly, the increase in torsion in response to exercise is attenuated with ageing (Burns *et al.*, 2008), perhaps due to an age-related decline in diastolic function and functional capacity (George *et al.*, 2010) or chamber compliance (Fujimoto *et al.*, 2012).

Systolic function is also augmented in response to exercise. For example, ejection fraction is increased and end-systolic volume (ESV) is reduced (Rerych *et al.*, 1978). Recent investigation into the kinetics of LV mechanics during exercise has found an increase in systolic longitudinal strain and LV twist upon exercise initiation (Doucende *et*

al., 2010; Izem *et al.*, 2019). In untrained individuals, a plateau in LV SV is attained at moderate intensity exercise, (Higginbotham *et al.*, 1986) and a decline in SV may even be observed at peak exercise (Stringer *et al.*, 2005; Stickland *et al.*, 2006*b*). In contrast, SV increases progressively with increasing intensity in endurance-trained individuals (Gledhill *et al.*, 1994; Stickland *et al.*, 2006*b*), due to an augmented venous return and a subsequent elevation in LV EDV (Higginbotham *et al.*, 1986). The greater LV EDV and SV achieved in athletes may be due to changes in the Frank-Starling mechanism (Levine *et al.*, 1991) and other inotropic mechanisms that may be enhanced with endurance training, outlined in Chapter 2.2.4.

2.3.2 Right Ventricular Response to Endurance Exercise in a Normal Heart

Increases in cardiac output during exercise have historically been attributed to increases in heart rate, LV function, and vasodilation of the systemic circulation (La Gerche *et al.*, 2017). However, since the cardiovascular system is composed of two circulations in series, output from the LV is equal to that of the RV. As such, there is now recognition of the role in which the RV and pulmonary vasculature have upon the regulation of exercise-induced increases in cardiac output (La Gerche *et al.*, 2017).

It is evident that the RV has substantial systolic reserve that is recruitable during exercise. Echocardiographic assessment of the RV has consistently demonstrated an increase in indices of systolic performance during exercise (La Gerche *et al.*, 2011; Guazzi *et al.*, 2013). As such, RV systolic pressure increases considerably during moderate-to-intense exercise (Guazzi *et al.*, 2013). Using invasive methods to assess RV function, (Cornwell *et al.*, 2020) recently demonstrated a three- to fourfold increase in RV end-systolic elastance (Ees) from rest to peak exercise in healthy individuals. Several recent studies have shown that RV systolic reserve is normally adequate to compensate for increases in arterial load (Ea) associated with brief exercise (Spruijt *et al.*, 2015; Singh *et al.*, 2019; Cornwell *et al.*, 2020), such that arterio-ventricular coupling is maintained

(Ees:Ea within 1.5 to 2.0; i.e., force of contraction matches the increase in load, such that SV is maintained). Nonetheless, it has been proposed that the RV may be the 'weak link' which ultimately limits augmentation of cardiac output (La Gerche *et al.*, 2017). This limitation may be due to; i) 'in series' ventricular interaction (i.e., the relation between RV and LV output, the two necessarily being equal over time), and/or ii) 'direct' or 'in parallel' ventricular interaction (i.e., the complex interaction between the direct filling and function of one ventricle on the output of the other, related to the physiology of the interventricular septum and pericardial constraint).

Pressure is a primary determinant of afterload and, as mentioned previously, pulmonary artery pressure is substantially elevated during intense exercise. Relative to the LV, increases in load during exercise are greater for the RV (e.g., 166% increase in PASP vs 36% increase in SBP), which results in a greater exercise-induced increase in RV wall stress (125.2%) relative to LV wall stress (13.6%) (La Gerche *et al.*, 2011; Lakin *et al.*, 2021). This disproportionate haemodynamic loading was further confirmed in a mice model, which evidenced a greater negative impact of acute exhaustive exercise on the RV compared to the LV (Lakin *et al.*, 2021). These differential effects of prolonged exercise on the RV and LV in mice were attributed to a dramatic rise in LV end-diastolic pressure near exhaustion. Whilst increasing preload helps to augment SV (via the Frank-Starling mechanism), increasing LV end-diastolic pressure increases the afterload of the RV (via in series interaction), which requires a greater right ventricular systolic pressure (RVSP) to facilitate RV ejection. Indeed, increasing LV end-diastolic pressure is directly transmitted upstream to the pulmonary circulation, increasing pulmonary artery diastolic pressure (PADP) by a 1:1 ratio (Naeije, 2013; Reddy *et al.*, 2018). During exercise, the disproportionate influence of increasing pressure may be further exacerbated by a physiological flow-dependent pressure gradient between the RV and pulmonary vasculature (Wright *et al.*, 2019). It is possible that RV systolic reserve therefore limits SV

and subsequently cardiac output augmentation during intense exercise. Alternatively, an increase in RV filling, combined with greater fluctuations in intrathoracic pressure, may cause a leftward shift of the interventricular septum, as pericardial constraint inhibits further distension of the RV free wall (Atherton *et al.*, 1998). It is strongly suggested that pericardial constraint has an important influence on cardiac function during exercise, which may be exacerbated among endurance-trained individuals (Reeves *et al.*, 1990; Stickland *et al.*, 2006*b*).

2.4 Cardiovascular Remodelling Associated with Endurance Training

Cardiac enlargement in trained athletes was first documented over a century ago (Henschen, 1899). Numerous researchers since then have helped to establish normal features of the endurance athlete's heart, including electrical, functional and structural cardiac adaptations (Vinereanu *et al.*, 2001; Maron, 2005; Oxborough *et al.*, 2012*b*; Sharma *et al.*, 2017; Lord *et al.*, 2018). Sinus bradycardia, respiratory sinus arrythmia, and biatrial and biventricular enlargement with mild-to-moderate wall thickening have become hallmark features of the endurance athlete's heart (Baggish & Wood, 2011; Galderisi *et al.*, 2015; Sharma *et al.*, 2017). Until relatively recently, research has been focused upon the LV, with the RV often referred to as the "forgotten chamber" due to the difficulty to image owing to its complex morphology (Rigolin *et al.*, 1995; Kossaify, 2015; Marwick & Chandrashekhar, 2017; Tretter & Redington, 2018). Technological advances in non-invasive imaging techniques such as echocardiography and cMRI, have provided new insights into RV structure and function.

Long-term cardiovascular adaptations to endurance training are epitomised by an increase in maximal oxygen uptake, which is associated with a high maximal cardiac output. As maximal heart rate is unchanged, or lower compared with untrained controls

(Zavorsky, 2000), the augmentation in cardiac output is solely due to an elevated SV (Ekblom & Hermansen, 1968). Such changes in SV are mediated by structural and/or functional remodelling of the heart, and by changes in blood volume associated with exercise training.

2.4.1 Systemic and Pulmonary Vascular Adaptation to Endurance Training

The impact of aerobic exercise training on capillary growth is well established (Andersen & Henriksson, 1977; Saltin & Gollnick, 2011). It is also now considered that endurance athletes possess enlarged arterial vessels (both resistance and conduit) presumably to facilitate persistent and high blood flows during exercise, which has been reviewed in detail previously (Green *et al.*, 2012). Such vascular adaptations are highlighted by the finding that exercise training improves oxygen uptake and cardiac output during exercise, whilst mean arterial pressure is unaltered (Clausen, 1977), suggesting a reduction in vascular resistance (Green *et al.*, 2017).

Pulmonary vascular remodelling with endurance training has not been previously reported, despite the substantial haemodynamic stimuli associated with aerobic exercise. RV ejection and pulmonary artery systolic pressure (PASP) are tightly coupled (Pinsky, 2016). As such, a greater SV and pulsatile blood flow among endurance-trained individuals can increase PASP, as evidenced by the cross-sectional echocardiographic screening of 370 endurance athletes in Italy (D'Andrea *et al.*, 2011). In this large cardiac screening study, PASP was elevated in endurance athletes compared with both non-athletic controls and strength athletes, and an upper physiological limit of 40 mmHg was proposed. This guideline has since been implemented in the expert consensus recommendations for the athlete's heart (Galderisi *et al.*, 2015). This "physiologic phenomenon" was proposed to result from a proportionally greater SV in endurance athletes, which was determined by a positive correlation between PASP and SV. Whilst correlation does not necessarily equal causality, the relationship between SV and PASP has been well described (**Figure 6**)

(Harvey *et al.*, 1971). Utilising this relationship, it is possible to mathematically estimate the SV required to generate a PASP of 40 mmHg and speculate as to whether such high pressures in athletes are truly a physiologic consequence of high SVs.

In a population of 44 healthy volunteers (aged 17 - 83 years), invasive haemodynamic measurements were obtained at rest, during exercise, and whilst either recumbent or seated (Harvey *et al.*, 1971). Both systolic and mean pulmonary pressure increased proportionally to SV and pulmonary vascular compliance, at any given diastolic pulmonary pressure PADP. The following equation was subsequently produced, predicting PASP in healthy individuals:

$$(PASP = 1.41 + 1.61 * PADP + 0.09\ SV)$$

However, rearranging the same equation, it can predicted that a SV of 250 ml would be required to generate a PASP as high as 40 mmHg, assuming a constant PADP of 10 mmHg:

$$[40\ mmHg\ -1.41 - (1.61 * 10)]/0.09 = 250\ ml$$
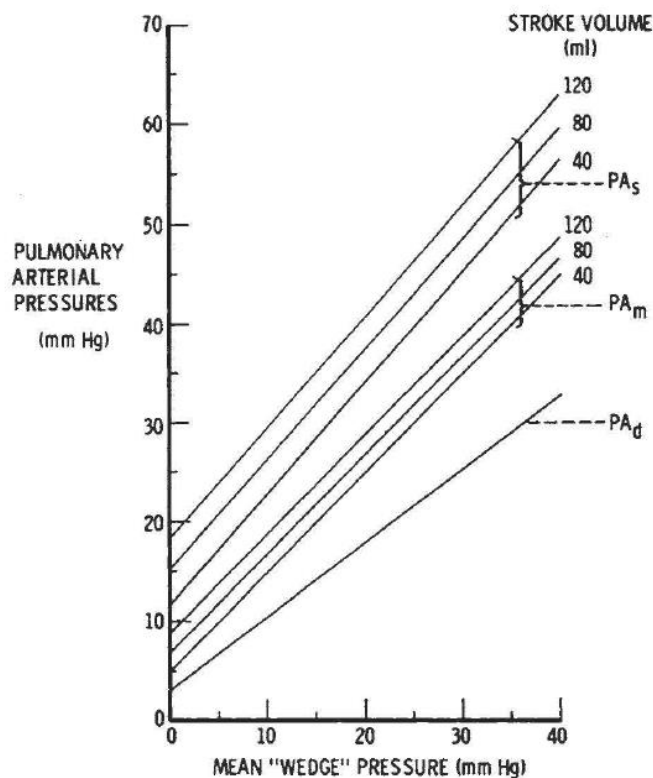
Figure 6. Schematic representation of the effect of left heart filling pressure and stroke volume on pulmonary arterial systolic, mean, and diastolic pressures.

Taken from Harvey et al. (1971)

SV, in even the most well-trained athletes, rarely exceeds 150 ml (La Gerche *et al.*, 2011; Utomi *et al.*, 2013) and averaged 100 ± 6 ml in the Italian screening study (D'Andrea *et al.*, 2011). Therefore, in addition to an elevated SV, PASP values as high as 40 mmHg in some athletes may be influenced by other factors, such as elevated PADP (PAWP or LAP) and/or pulmonary vascular remodelling. However, evidence suggests that endurance athletes typically have normal resting left atrial pressure and hence should have normal resting PADP (between 8 mmHg to 11 mmHg (Levine *et al.*, 1991; Stickland *et al.*, 2006*a*; Wright *et al.*, 2015; Esfandiari *et al.*, 2019; Buchan *et al.*, 2019). Pulmonary vascular remodelling in athletes, however, remains a controversial topic that is discussed below.

Traditionally, the capacity of the pulmonary system was assumed to exceed the demands required for ventilation and gas exchange during exercise, and hence was thought to be insensitive to exercise training (McKenzie, 2012). However, pulmonary vascular distensibility (i.e., the percentage increase in diameter per unit change in transmural pressure) has recently been suggested as an independent predictor for aerobic capacity (Lalande *et al.*, 2012; Malhotra *et al.*, 2016). If this is true, then it may be expected that highly-trained endurance athletes have the greatest PV distensibility, contributing to pulmonary vascular reserve capacity and perhaps alleviating the afterload that the RV confronts. This hypothesis, however, is yet to be experimentally investigated and a causal effect between exercise training and pulmonary vascular adaptation is currently missing. Furthermore, an argument for maladaptive remodelling has been speculated (Domenech-Ximenos *et al.*, 2020). The large increase in PASP during exercise may cause damage to the structurally vulnerable pulmonary vasculature, which could lead to fibrosis and scarring of the vessel wall. Pressures beyond ~25 mmHg may compromise pulmonary microvascular integrity (West, 2000) yet pressures are frequently reported beyond that during dynamic exercise (La Gerche *et al.*, 2010; Wright *et al.*, 2019). In animals with exceptionally high cardiac outputs relative to body mass (i.e., thoroughbred racehorses),

the associated pressure increase in the pulmonary vasculature results in the eventual rupturing of the capillaries, a term called 'exercise-induced pulmonary haemorrhaging'. The compromised pulmonary microvasculature integrity in these animals is clear, and bleeding from the nose (epistaxis; the original determinant of exercise induced pulmonary haemorrhaging) has been reported in racehorses for decades (Poole & Erickson, 2016). Nonetheless, whether microvascular capillary oedema or haemorrhage occurs in exercising humans is debated (Hopkins, 2010; Sheel & McKenzie, 2010).

2.4.2 Left Ventricular Remodelling with Endurance Training

2.4.2.1 Left ventricular structural remodelling in endurance athletes

Exercise-induced left ventricular remodelling has been extensively studied among endurance athletes and has been the subject of seven meta-analyses over the last 25 years (Fagard, 1996; Pluim *et al.*, 2000; Whyte *et al.*, 2004; Utomi *et al.*, 2013; Beaumont *et al.*, 2017*a*; Lord *et al.*, 2018; Wundersitz *et al.*, 2020). Consistent across all seven meta-analyses were findings of a greater absolute chamber size (LV internal diameter) and LV EDV among endurance-trained athletes, in addition to a moderate and proportional increase in wall thickness. These findings are commensurate with the eccentric LV hypertrophy proposed by (Morganroth *et al.*, 1975). Even when scaled for body size, LV diastolic volumes and SV remain greater among endurance-trained athletes vs non-athletic counterparts (Utomi *et al.*, 2013). The majority of investigation of exercise-induced cardiac remodelling, however, is cross-sectional in design, and therefore observational in nature.

Few studies of longitudinal design, relative to those of cross-sectional nature, have investigated the causal effect of endurance training on left ventricular remodelling. Nonetheless, the time-course of ventricular remodelling associated with endurance training has recently been studied, and the complexities highlighted. In response to a 12 month

progressive exercise training programme, Arbab_Zadeh et al, (2014) demonstrated that the LV undergoes concentric remodelling due to LV wall thickening during the first 6 months, when low intensity exercise was performed. Thereafter, when exercise intensity and duration was increased, the LV dilated (eccentric remodelling), restoring the mass to volume ratio. In contrast to this finding, in competitive male rowers, Weiner et al. (2015) found that the initial increase in LV mass was a result of an increased LV EDV without change in wall thickness during the 'acute augmentation phase' consisting ~13 hours of training per week for 90 days. Subsequent increases in LV mass were predominantly associated with an increase in LV wall thickness during the 'chronic maintenance phase' after 36 months of a similar training protocol. The apparent disparity between these studies was attributed to the underlying training status and relatively high training stimulus in the latter study. For example, Arbab_Zadeh et al, (2014) recruited twelve previously sedentary men and women, whom underwent a relatively low volume training programme beginning with 30 minutes of brisk walking 3-5 times per week, and almost reaching the training volume achieved by a 'typical' endurance athlete by the end of the 12 months. This population, and training programme, is vastly different to that of Weiner et al. (2015). Participants in the latter study were competitive athletes ($n = 12$) with a significant training history, reaching elite levels of training during the study. As such, it is possible that both studies reflect a normal continuum of phasic remodelling.

2.4.2.2 Resting left ventricular function in the endurance-athlete's remodelled heart

Enhanced left ventricular diastolic function has been extensively evidenced in endurance athletes with long-term training. Meta-analyses by both Pluim et al. (2000) and Utomi et al. (2013) report a greater E/A ratio (i.e., early (passive) to late (atrial contraction) diastolic filling), in comparison to untrained controls. Data aquired using tissue Doppler imaging (TDI) have also supported enhanced diastolic function in athletes, demonstrating a greater early (E'), and/or reduced late (A') tissue velocity at the septal and lateral wall annulus

(Caso *et al.*, 2000; Vinereanu *et al.*, 2002; Kasikcioglu *et al.*, 2005; D'Ascenzi *et al.*, 2011). This data is further supported by a recent meta-analysis which suggests that untwisting rate is greater in endurance athletes compared with untrained controls, indicating enhanced early diastolic filling (Beaumont *et al.*, 2017*a*). It is now well established that endurance training improves diastolic function (Kneffel *et al.*, 2011).

In contrast to left ventricular diastolic function, there is mixed evidence to support enhanced LV systolic function with long-term endurance training. LV ejection fraction is often used to assess systolic function; however, an eccentrically remodelled ventricle may require a lower magnitude of contraction to maintain normal SV, particularly at rest. Indeed, lower ejection fraction has frequently been reported in endurance athletes, despite significantly larger SV's compared with non-athletes (Galderisi *et al.*, 2015). Functional assessments of the myocardium have also been conducted by assessing tissue velocity, strain and strain rate. While there is evidence of enhanced systolic myocardial velocity in endurance athletes at rest (Baggish *et al.*, 2008*a*; D'Andrea *et al.*, 2010), recent meta-analyses reported no difference in speckle tracking derived indices of systolic function (i.e., global longitudinal strain) (Beaumont *et al.*, 2017*a*). However, LV twist was lower in elite endurance athletes compared with untrained controls (Beaumont *et al.*, 2017*a*). It has been proposed that lower systolic function among endurance athletes may reflect an enhanced functional reserve capacity, which may be utilised to assist with ejection and filling during bouts of exercise (Nottin *et al.*, 2008). In this regard, it is important to consider that many of the studies that have assessed LV function in endurance athletes have done so while the athlete is resting. However, for reasons alluded to above, assessment of cardiac function at rest may not fully represent the extent of adaptation. Relatively few investigations have compared training-specific adaptations during states of increased haemodynamic load, yet it is plausible that exercise-induced functional adaptations are specific to the repeated haemodynamic stimulus the ventricle is exposed to.

Levine et al. (1991) have eloquently shown that both young and older (Bhella *et al.*, 2014; Arbab-Zadeh *et al.*, 2014) endurance athletes have a more compliant, distensible LV, which operates on a steeper slope of the Frank-Starling curve (i.e., a greater increase in SV for any given increase in LV filling pressure; **Figure 7**). As such, it may be interpreted that athletes have an enhanced functional response to increasing preload, which may be considered an epiphenomena to structural remodelling resulting in a more compliant ventricle. Stimulus-specific functional remodelling (i.e., functional response to specific haemodynamic stimuli) has been recently proposed, and is discussed in more detail in **Chapter 2.7**, although few studies have experimentally tested this.
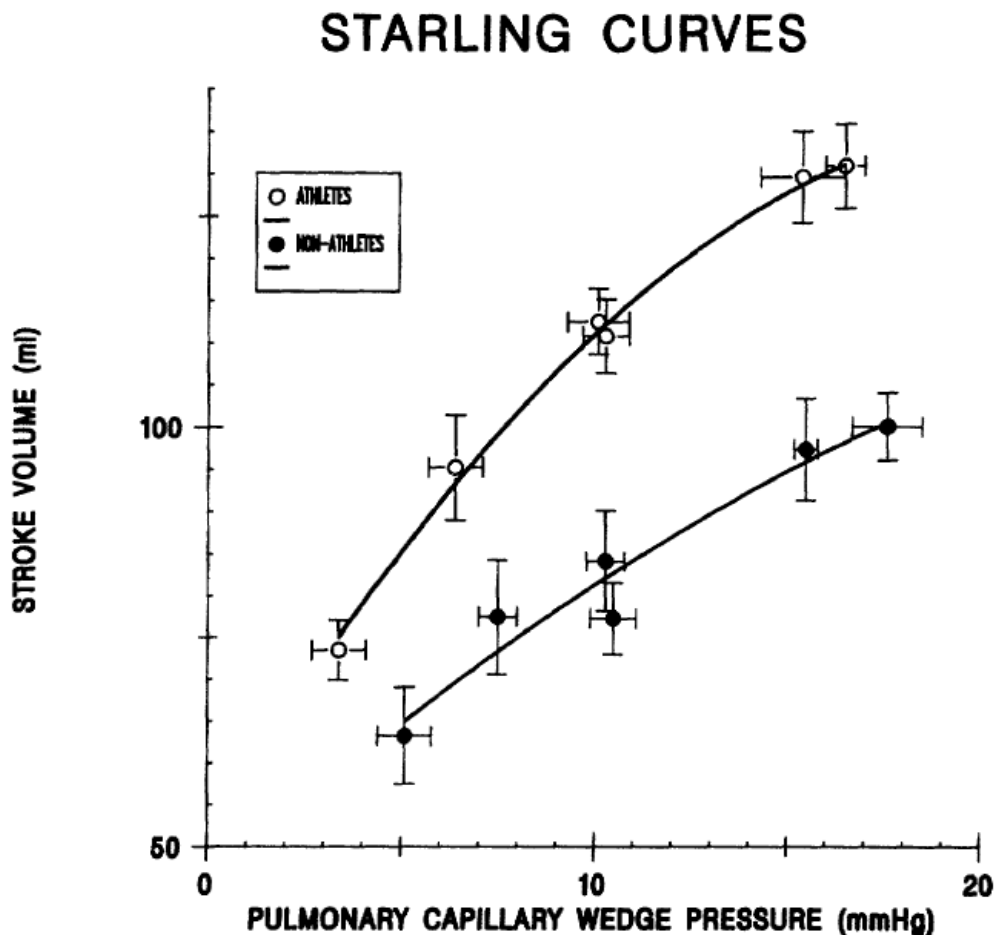
Figure 7. **Demonstrating the Starling curves relating pulmonary capillary wedge pressure to stroke volume in endurance athletes and nonathletes**.

Taken from Levine et al. (1991).

2.4.2.3 Region-specific left ventricular remodelling in endurance athletes

Inhomogeneity of wall motion across the cardiac muscle is common (Donovan *et al.*, 1995), and likely due to the anatomic arrangement of myocardial fibres resulting in a greater longitudinal contribution of the LV free wall when compared with the ventricular septum. Regional wall motion abnormalities have been identified in a variety of pathological conditions that share phenotypic resemblance to the athlete's heart. In patients with HCM, for example, tissue Doppler derived regional diastolic dysfunction (reflected by an e'/a' ratio <1) was detected in 25% of the myocardial segments (Cardim *et al.*, 2003). In many athletes, however, there appears to be no evidence of LV free wall motion abnormalities despite an increase in LV mass and volume (Pelliccia & Maron, 1997) and increased prevalence of hypertrabecularisation at the LV apex (Gati *et al.*, 2013, 2015; Abela & D'Silva, 2018). Recent meta-analysis of speckle-tracking derived strain parameters identified no differences between untrained controls and trained athletes (Beaumont *et al.*, 2017*a*). Further scrutiny, however, revealed a lower apical rotation in elite-level endurance athletes, perhaps signifying a functional reserve capacity as mentioned above, but also highlighting controversy with measures taken only in the resting state.

Regional wall motion abnormalities of the LV may arise following prolonged or intense exercise (Douglas *et al.*, 1990; La Gerche *et al.*, 2008) or in the presence of myocardial fibrosis (Eijsvogels *et al.*, 2016). Furthermore, a mild depression of LV circumferential strain occuring at the anteroseptal and inferoseptal segments has been observed following 90 days of endurance training in a cohort of young ($n = 20$; 20 ± 1 years of age) individuals (Baggish *et al.*, 2008*b*). This contrasts recent assessment in a group of lifelong ultra-endurance athletes ($n = 40$; 46 ± 8 years of age), whereby a greater circumferential and radial strain was observed at the basal inferoseptum and anteroseptum, when compared with non-active controls ($n = 24$; 46 ± 7 years of age) (Rothwell *et al.*, 2018). Interrogation of the basal inferoseptum and anteroseptum is highly relevant due to

the pattern of myocardial fibrosis frequently observed among endurance athletes, which appear to be predominantly localised to the RV insertion or "hinge" points (Wilson *et al.*, 2011; Prior & La Gerche, 2012; Eijsvogels *et al.*, 2016). Indeed, it has recently been identified that lifelong endurance athletes with myocardial fibrosis may have localised myocardial wall motion dysfunction specific to these fibrotic areas (Eijsvogels *et al.*, 2017). Nonetheless, the clinical consequences of the appearance of fibrotic regions in lifelong athletes, via late gadolinium enhancement on MRI, remains unclear and beyond the remit of this thesis. The contradictory findings between Baggish et al. (2008*b*) and Rothwell et al. (2018) may be due to the vast difference in age between study populations and/or the training stimulus (competitive rowers during a 90 day period of training intensification vs. comparison of lifelong ultra-endurance runners vs. age-matched sedentary controls, respectively). As such, similar to the exercise-induced phasic remodelling that has been previously suggested (Chapter 2.4.2.1), the disparity in findings may reflect acute vs long term remodelling patterns. It is also possible that the adaptation of the RV may also influence septal mechanics (Baggish *et al.*, 2008*b*), since RV fibres traverse into the interventricular septum and consitutite a large portion of septal structure (Ho & Nihoyannopoulos, 2006), however this hypothesis is to be experimentally tested. Furthermore, this theory is not supported by another study, which found no significant differences in regional LV longitudinal strain at the RV insertion points of the septum, despite structural RV adaptation, between a veteran cohort of elite endurance athletes (*n* = 33; aged 47 ± 8) and age, height and weight matched nonathetic controls (*n* = 33; aged 46 $\pm$ 9, exercising < 3hours/week) (Bohm *et al.*, 2016). Using speckle-tracking echocardiography to examine regional adaptation, RV basal longitudinal strain was the only region found to be significantly lower in the endurance athletes. Interestingly, no evidence of myocardial fibrosis was found in this study, though evidenced in others (Breuckmann *et al.*, 2009; Wilson *et al.*, 2011), which may confound comparisons of regional function in

veteran athletic cohorts. The development of myocardial fibrosis (as assessed via late gadolinium enhancement via MRI) athletes is not entirely predictable, however, and appears to be prevalent in a minority of healthy, asymptomatic individuals (Baggish, 2018). Notably, elite veteran athletes recruited by Bohm et al. (2016) had a far shorter training history (29 ± 8 years) than those recruited by Wilson et al. (2011) (43 ± 6 years), which may contribute towards discrepencies, although others have suggested that life-long high dose exercise is not associated with focal myocardial fibrosis (Abdullah *et al.*, 2016). Rather, the combination of i) exercise dose and the associated haemodynamic demand, and ii) predisposition to exercise-induced systolic hypertension (Tahir *et al.*, 2018) and/or iii) exercise continuation coupled with subclinical infection (Hosenpud *et al.*, 1987; Baggish, 2018). Further work is required to clarify the pathogenesis as well as the clinical relevance of non-ischaemic fibrosis, and how this may influence regional function in the heart.

2.4.3 Right Ventricular Remodelling with Endurance Training

2.4.3.1 Right ventricular structural remodelling

Structural remodelling of the RV in response to long-term endurance training has been well characterised. Echocardiographic (D'Ascenzi *et al.*, 2017*a*) and cMRI assessments of the RV in endurance athlete's (D'Ascenzi *et al.*, 2019) have identified increased mass, greater ventricular volumes, ventricular enlargement, and dilatation of the ventricular cavity and outflow tract. The increased RV cavity dimensions in endurance athletes leads to a higher RV sphericity index (i.e., the ratio of RV transversal diameter to RV length) (D'Andrea *et al.*, 2003, 2013). Furthermore, recent three-dimensional assessment of the athlete's heart suggests that RV myocardial adaptation is characterised by an increased relative contribution of longitudinal motion and a decrease in radial motion, at rest (Lakatos *et al.*, 2018). Interestingly, the RV appears to remodel to a greater extent than that of the LV, which may reflect a disproportionate increase in right-sided wall stress during intense or prolonged exercise (La Gerche *et al.*, 2017; Lakin *et al.*, 2021). The complex geometry of

the RV, including its crescentic shape and thin wall, may contribute to considerable wall-stress non-uniformity. Indeed, adaptation specifically affecting different regions of the RV has been noted. For example, dilatation at the base is commonly observed (La Gerche *et al.*, 2010, 2011), with bulging of the basal RV free wall (Prior & La Gerche, 2012; Bohm *et al.*, 2016) and displacement (Brosnan *et al.*, 2015) and hypertrabeculation of the apex (Oxborough *et al.*, 2012*b*; D'Andrea *et al.*, 2013; D'Ascenzi *et al.*, 2017*a*) frequently reported in well-trained athletes.

2.4.3.2 Resting right ventricular function in the endurance-athlete's remodelled heart

In contrast to the literature supporting structural remodelling of the RV with endurance training, fewer studies have examined adaptations of RV function. Similar to the LV, RV systolic function was preserved or slightly reduced in athletes when assessed using ejection fraction or fractional area change, despite an increase in SV (La Gerche *et al.*, 2011; D'Ascenzi *et al.*, 2017*b*, 2017*a*). This may be explained by the fact that a larger RV requires a smaller ejection fraction to achieve the same SV of a smaller RV. Since RV ejection is predominantly mediated by longitudinal shortening (Ho & Nihoyannopoulos, 2006), conventional assessment of longitudinal myocardial displacement (TAPSE) and velocity (S') are frequently used to assess RV systolic function. Several cohort studies have demonstrated augmented systolic function (TAPSE and S') in athletes compared to controls, (Caso *et al.*, 2002; D'Ascenzi *et al.*, 2013; D'Andrea *et al.*, 2013) although others have found that systolic function is mildy reduced (Simsek *et al.*, 2013; La Gerche *et al.*, 2015; Bohm *et al.*, 2016; Doronina *et al.*, 2018), creating controversy in this area of research. However, these parameters do not correlate well with ejection fraction if chamber remodelling does not equally affect the basal, mid and apical portions of the RV (Seo & Lee, 2018), as may occur in with following endurance-based training. Currently, expert consensus guidance for the assessment of the athlete's heart provides recommendations of normal FAC and TAPSE as measures of RV function only (Galderisi *et al.*, 2015), which

are not dissimilar to reference values provided for the general population (Rudski *et al.*, 2010). Over the last 10 years, longitudinal strain analysis (i.e., deformation of the myocardium from its initial length) of the RV has been increasingly utilised. Strain analysis is relatively size and load dependent and may be sensitive to subtle RV abnormalities. Teske et al. (2009) reported that RV strain and strain rate were lower in healthy athletes, particularly in those who were highly trained and had greater RV dilation. However, following this observational study, free wall longitudinal strain in endurance athletes has been reported to be greater (Esposito *et al.*, 2014), lower (Stewart *et al.*, 2020) or not different, compared with untrained controls (La Gerche *et al.*, 2012*a*; Pagourelias *et al.*, 2013). Comprehensive, quantitative analysis of literature reporting data on systolic RV function in athletes is yet to be conducted. Such analysis would have an important impact on clinical practice, whereby structural remodelling can be considered in concert with normal functional adaptation in order to differentiate pathological remodelling with physiological remodelling.

2.4.3.3 Region-specific right ventricular remodelling

Due to the aforementioned anatomical complexity of the RV, myocardial adaptation to haemodynamic loading with exercise training may promote non-uniform region-specific adaptation. For example, recent evidence suggests that resting myocardial deformation at the RV base is lower among endurance athletes (Teske *et al.*, 2009), but deformation at the apex is greater (La Gerche *et al.*, 2012*a*), in comparison to non-athletes. Morphological differences between the smooth basal inlet and the trabeculated apex, including myofiber alignment, local radii of curvature, and relative dimensions, may promote a basal portion of the RV that is more sensitive to increases in wall stress during exercise, which promotes preferential dilation of the basal segment and subsequently reduced strain (Teske *et al.*, 2009). In support of this concept, mathematic modelling studies of the LV predict that peak longitudinal strain will decrease with increasing ventricular size (Sutherland *et al.*,

2004). Elevated preload conditions at rest, due to significant blood volume expansion (Convertino, 1991), may also partially explain the lower RV basal deformation among athletes. However, resting data may not reflect the full extent of cardiac remodelling; it is possible that regional RV function, and its response to the repetitive haemodynamic load caused by endurance exercise, may also adapt.

Exercise load is clearly an important determinant of RV remodelling, and there is speculation of a threshold for training load beyond which RV adaptation may become detrimental, potentially causing impaired segmental myocardial function (Benito *et al.*, 2011; Sanz-de la Garza *et al.*, 2017*b*; Lakin *et al.*, 2021). However, mechanistic investigation of adverse RV remodelling associated with vigorous exercise training remains confined to rodent models under highly stressful conditions, and therefore translation to humans remains speculative. In addition to signs of fibrosis, these animal models provide further evidence of segment-specific reduction in function at the RV base, and reduced RV contractility at rest. However, since there is tight coupling between RV elastance (contractility) and pulmonary arterial elastance (RV afterload) throughout a range of physiological settings (Tello *et al.*, 2019; Cornwell *et al.*, 2020), the low RV contractility at rest may reflect a maintenance of ventricular-arterial coupling, by matching contractility to low afterload. Further assessment of the functional RV response is crucial to improving our understanding of exercise-induced RV remodelling.

2.5 Haemodynamic Response to Resistance Exercise

2.5.1 Left Ventricular Response to Resistance Exercise

The primary role of the LV during exercise is to maintain forward blood flow in the face of high downstream arterial resistance (Shave *et al.*, 2019), which is recognised to exceed 300 mmHg during heavy resistane exercise (MacDougall *et al.*, 1985, 1992; Haykowsky *et al.*,

2001). This dramatic rise in blood pressure is attributed to; i) the independent effect of the Valsalva manoeuvre (MacDougall *et al.*, 1985), ii) the mechanical compression of blood vessels from muscular contraction (Barcroft & Millen, 1939; Tonnesen, 1964), and iii) the autonomic nervous system (including the exercise pressor reflex, arterial baroreflexes, and 'central command') (Rowell, 1992). The Valsalva manoeuvre causes an abrupt increase in blood pressure by raising intrathroacic pressure, which subsequently compresses the great vessels (MacDougall *et al.*, 1985). This manoeuvre is unavoidable at approximately 80 - 85% of maximal voluntary contraction, but does provide a mechancial advantage during resistance exercise by stabilising the trunk (MacDougall *et al.*, 1992). In addition, the exercise pressor reflex also stimulates an increase in blood pressure. This reflex has two functional components, the muscle metaboreflex and the muscle mechanoreflex, which are mediated via the activation of chemically or mechanically sensitive receptors, respectively, located within the skeletal muscle (Joyner & Casey, 2015). The exercise pressor reflex mediates autonomic adjustments to the cardiovascular system by enhancing sympathetic output, while simultaenously reducing parasympathetic activity in order to increase blood flow to the contracting skeletal muscle (Victor *et al.*, 1989; Vissing *et al.*, 1991). Resultant efferent activity increases blood pressure, heart rate and LV contractility (Grotle *et al.*, 2020). In conjuction with these peripheral components of the autonomic response, 'central command' (i.e., activation of the cardiovascular control areas located in the medulla) establishes a basal level of sympathetic activity, which is thought to be closely linked to the intensity of the effort (Nobrega *et al.*, 2014). The increased sympathetic outflow to the heart and skeletal muscle vascular bed increases perfusion pressure and redistributes blood flow towards the contracting muscle (Grotle *et al.*, 2020).

It is a long-held belief that the elevated chamber pressure associated with resistance exercise may be a potent stimulus for LV remodelling. Indeed, using the Law of LaPlace to define afterload (and wall stress: $\sigma = \frac{p \times r}{h}$), it is intuitive that a substantial increase in

pressure (assuming little or no change in wall thickness and chamber radius) would result in an elevated wall stress. However, it is more appropriate to consider transmural pressure (i.e., the pressure between both sides of the ventricular wall) for the calculation of wall stress rather than internal chamber pressure alone. Usually, systemic arterial pressure adequately represents transmural pressure, because intrathoracic pressure is normally low (Mahmood & Pinsky, 2018). However, intrathoracic pressure increases substantially during resistance exercise when performed with a valsalva maneovre (Haykowsky *et al.*, 2001). Therefore, LV wall stress calculated using transmural pressure is lower during resistance exercise with a Valsalva maneovre, than would be predicted by BP alone (Lentini *et al.*, 1993; Haykowsky *et al.*, 2001). This was elegantly demonstrated by (Haykowsky *et al.*, 2001), which remains the only study to date to measure transmural wall stress during static exercise with invasive haemodynamic and intrathoracic monitoring (**Figure 8**). Nonetheless, it has been argued that internal LV chamber pressure (exclusion of intrathoracic pressure) is more closely associated with LV systolic mechanics (i.e., torsion) than transmural LV wall stress, due to the observed decline in LV torsion during leg press exercise with a Valsalva maneovre (Stohr *et al.*, 2017). Twist impairment has also been evidenced during isometric handgrip exercise, together with a reduction in SV (Weiner *et al.*, 2012; Wasfy *et al.*, 2019); whereas, during an isometric knee extention, twist was preserved (Beaumont *et al.*, 2017*a*). However, as intrathoracic pressure was not monitored in the aforementioned studies, it is possible that the high intrathoracic pressures exerted a direct effect on cardiac function, as both the heart and lungs compete for space within the thoracic cavity. Consistent with this, (Claessen *et al.*, 2014) observed a 25% decrease in LV SV during a Valsalva maneuvre using cMRI. Therefore, a causal relationship between increasing internal LV chamber pressure and twist impairment cannot be made, due to the potentially confounding influence of intrathoracic pressure.

Irrespective of wall stress, static exercise alters cardiac haemodynamics. LV volumes are reduced during sustained static exercise (Haykowsky *et al.*, 2001; Alegret *et al.*, 2015), which is likely due to a rise in intrathoracic pressure and concomitant vena cava compression, subsequently causing diminished venous return (Alegret *et al.*, 2015). As such, the reduction in SV often associated with resistance exercise may be considered, at least partly, a consequence of the reduction in preload. However, a compensatory increase in LV contractile function is likely to occur, due to the maintenance of ejection fraction and lower end-systolic cavity size (Haykowsky *et al.*, 2001). Mechanisms intrinsic to the myocardium may also mediate an increase in contractility with increasing afterload. Alterations in caldium handling proteins and calcium channels are likely to be mediated an increase in afterload (Anrep effect), an increase in heart rate (Bowditch effect) and an increase in coronary perfusion (Gregg phenomenon), as outlined in Chapter 2.2.1.
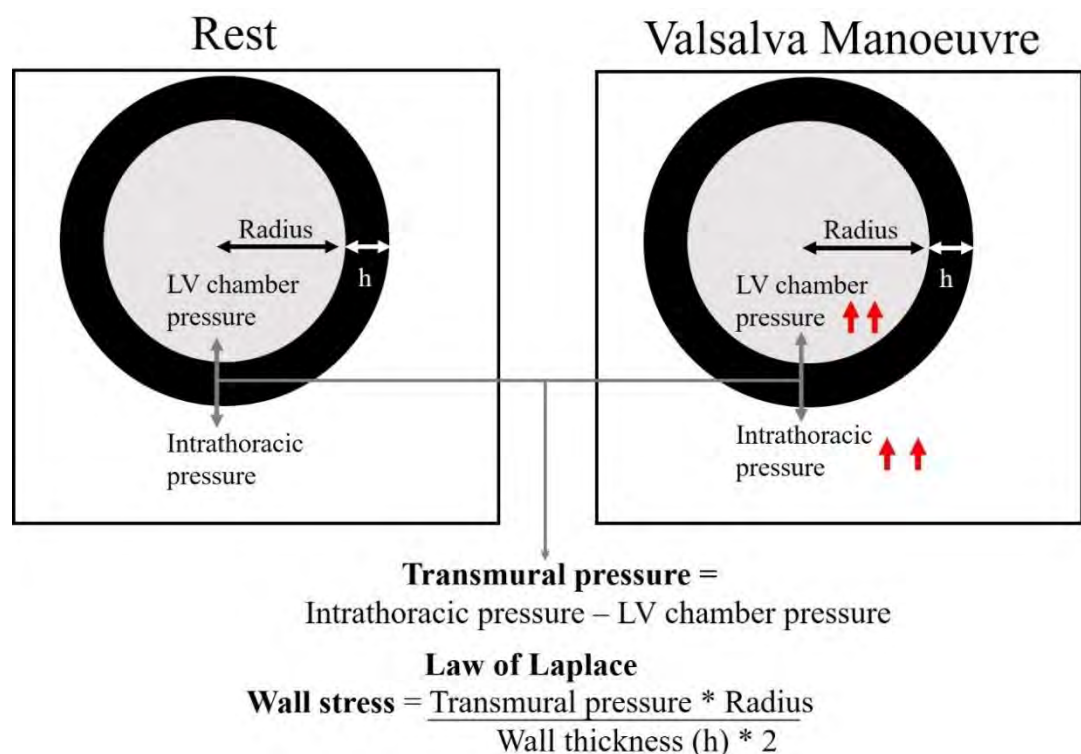
Figure 8. **Summary figure to depict the parameters determining LV transmural wall stress according to the Law of LaPlace and the associated changes following a Valsalva manoeuvre during resistance exercise.**

According to Haykowsky et al. (2001), the increase in LV chamber pressure during resistance exercise with obligatory Valsalva maneovre results in a similar increase in intrathoracic pressure. As such, transmural pressure, and therefore wall stress, is relatively unchanged.

In summary, resistance exercise is associated with large increases in systolic and diastolic systemic arterial pressures, in addition to elevations in LV transmural pressure and wall stress, when performed in the absence of the Valsalva maneuvre. LV contractility is also increased due to sympathetic activation induced by the exercise pressor reflex, central command, and mechanisms intrinsic to the myocardium that influence calcium handling (**Figure 9**). However, it is currently unknown whether repetitive, intermittent initiation of such mechanisms elicit an adaptation in how the heart responds to an abrupt increase in LV afterload.
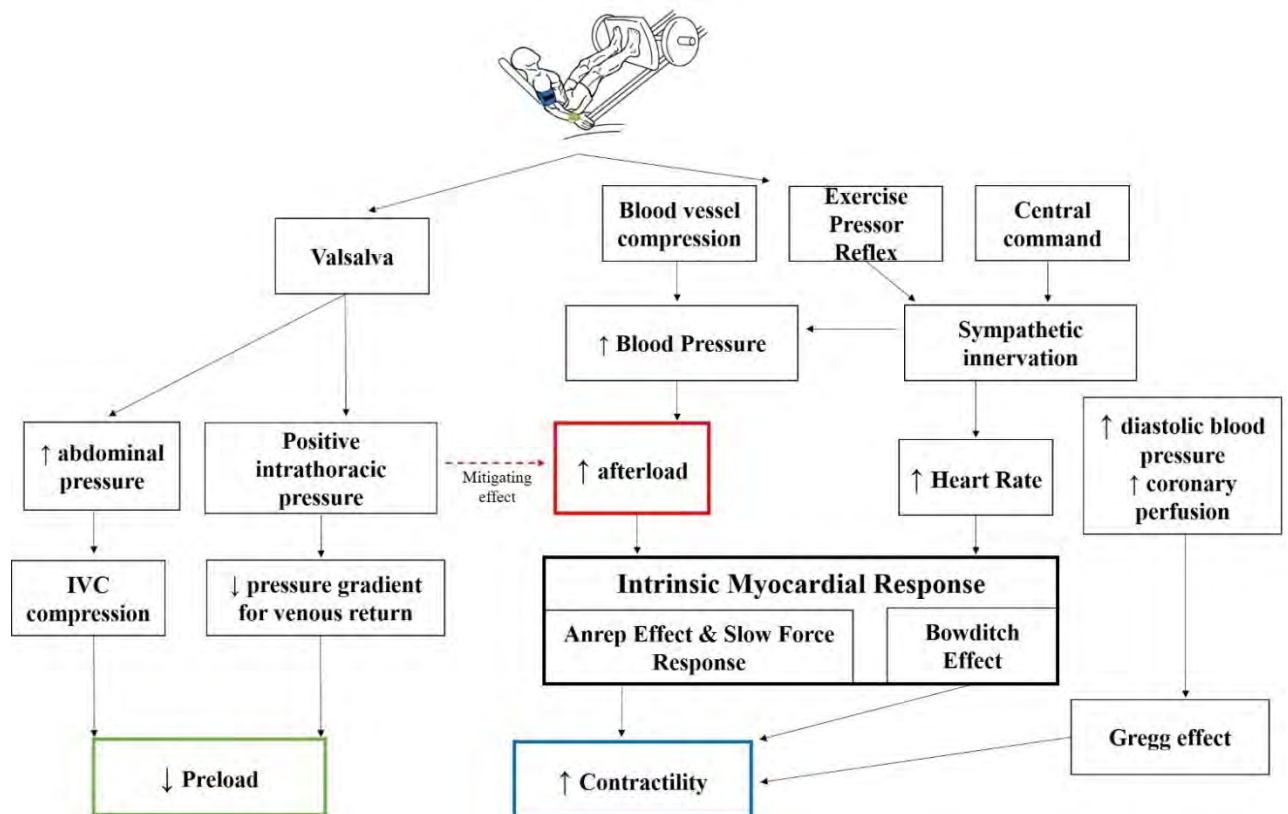
Figure 9. **Summary of proposed key mechanisms resulting in a change in LV haemodynamic loading conditions during isometric resistance exercise**.

Red dashed line indicates the mitigating effect in which an increase in intrathoracic pressure has on transmural pressure, and subsequently LV afterload, during a Valsalva maneovre.

2.5.2 Right Ventricular Response to Resistance Exercise

Since the heart essentially consists of two pumps working in-series (i.e., left and right ventricle), pressure (and volume) on one side of the heart can substantially affect the other side (Belenkie *et al.*, 2001). As such, an increase in systemic blood pressure during resistance exercise may also amplify RV afterload via series interactionFor example, during resistance exercise, the changes in the systemic circulation (namely a prodigious increase in diastolic and systolic blood pressures) interact with LV diastolic properties (i.e., compliance and stiffness), increasing left atrial pressures which, in turn, may be transmitted through the pulmonary circulation to the right heart. Furthermore, lung inflation above functional residual capacity prior to Valsalva may impede blood flow through pulmonary vessels, particularly intraalveolar capillary vessels which will be compressed (West, 2000). Extraalveolar capillaries, in contrast, are stretched, however the net influence would be an increase in pulmonary vascular resistance. Indeed, the response of the pulmonary vasculature at the onset of the valsalva maneovre appears to parallel that of the systemic vasculature, albeit to a lesser absolute magnitude of change in pressure. At the start of the valsalva manoevure, pulmonary artery systolic and diastolic pressures increase (by around 25-40 mm Hg) (Stone *et al.*, 1965; Fox *et al.*, 1966). Intriguingly, the increase in pumonary pressures are consistent with the increase in upstream pulmonary wedge pressure (i.e., left atrial pressure), which increases by the same magnitude as intrathoracic pressure (Stone *et al.*, 1965). As work continues pulmonary artery pulse pressure decreases, likely owing to the associated reduction in venous return and hence reduction in RV stroke volume (Fox *et al.*, 1966). Nonetheless, a net redution in transmural pulmonary artery pressure (i.e., pressure within the pulmonary artery relative to intra-thoracic pressure) has been documented as a consequence of a Valsalva (Charlier *et al.*, 1974; Pinsky, 1984), which argues strongly against an amplified RV wall stress, particularly considering the pronounced reduction in venous return (and therefore RV cavity size). Therefore, while the

RV may be exposed to haemodynamic changes during resistance exercise, when performed in the presence of a Valsalva maneuvre, the stimulus is unlikely to be sufficient for remodelling.

Few studies have assessed the acute or long-term impact of resistance exercise on the RV. However, since large fluctuations in intrathoracic pressure are often associated with resistance exercise, the thin-walled, low pressure RV may be particularly susceptible to diminished venous return. Indeed, Alegret et al. (2015) have shown using cMRI that volume reductions in the RV were more evident than the LV during static exercise. This has been further substantiated using cMRI during a Valsalva maneuvre, demonstrating that reductions in volume were proportionately greater for the RV than for the LV (Claessen *et al.*, 2014). Given the moderate increase in cardiac output,the reduction in RV volumes, and the minimal change in transmural pulmonary pressure, it is likely that RV afterload increases minimally, if at all, and may explain why extensive RV remodelling has not been associated with resistance training (Spence *et al.*, 2013*a*).

Haemodynamics during the valsalva phase of resistance exercise represents a relatively transient phase. Similar to the aorta, the volume and pressure of the pulmonary vessels increase upon release of the Valsalva (Eckberg, 1980) and a pressure overshoot can be observed in the pulmonary arteries, owing to the restoration of venous return and associated increase in stroke volume (Fox *et al.*, 1966). As such the recovery period after an intense exertion, with concomittant rise in both RV pressure and volume, may have the greatest impact upon RV wall stress, however this is yet to be quantitatively substantiated. Furthermore, resistance-type exertion is not always accompanied by a valsalva; for example prolonged exertion at relatively low-moderate intensity. Perhaps this type of activity, sufficient to elevate left atrial, pulmonary vascular, and RV pressures, without significanty changing intrathoracic pressure, and without impeding upon venous return may evoke a substantial haemodynamic challenge for the RV. Similar to the LV, further research is

required to understand the consequence of different types and phases of resistance exercise on RV haemodynamics. As highlighted by Naylor et al. (Naylor *et al.*, 2008), few studies have assessed the haemodynamic stimuli for RV or LV remodelling during different types, volumes and intensities of resistance exercise, although this is crucial to our understanding this integral component of the Morganroth hypothesis. To date, this remains an important area of future research.

2.6 Cardiac Remodelling Associated with Resistance Training

2.6.1 Systemic and Pulmonary Vascular Adaptation in Resistance Athletes

As described above, resistance exercise exerts a transient increase in blood flow with prodigious and rapid increases in arterial pressure (MacDougall *et al.*, 1992; Thomas *et al.*, 2020). However, research pertaining to the acute effect and chronic remodelling of peripheral vasculature is lacking. Most studies investigating exercise-induced vascular remodelling have predominantly focused on those associated with endurance-training. Nonetheless, six months of upper limb dominant resistance training resulted in structural remodelling of the brachial artery (increased peak diameter), but not the femoral artery (Spence *et al.*, 2013*b*). Conversely, lower body endurance training resulted in structural and functional remodelling of the femoral artery, but not the brachial. A finding supported by cross-sectional follow-up study by the same group, assessing elite endurance and resistance athletes (Naylor *et al.*, 2021). Conversely, resistance training has also been shown to have a deleterious effect on systemic arterial compliance (Otsuki *et al.*, 2007; Babaee Bigi & Aslani, 2007) and measures of arterial stiffness in highly-trained athletes (Kasikcioglu *et al.*, 2004; D'Andrea *et al.*, 2012; Kim *et al.*, 2015). Whether these findings are due to the haemodynamic stimulus associated with resistance training, or due to counfounding influences such as diet, lifestyle, underlying disease, or ergogenic aids, is

currently unknown. No changes in pulmonary vascular haemodynamics have been reported following resistance training, however given the limited transmural load that the pulmonary circuit is exposed to during resistance exercise (**Chapter 2.5.2**), pulmonary vascular adaptation is not to be expected.

2.6.2 Left Ventricular Remodelling with Resistance Training

2.6.2.1 Left ventricular structural remodelling

Following the observation made by (Morganroth *et al.*, 1975), LV structural remodelling among resistance athletes has been well studied, but remains a controversial topic. Teleologically, concentric remodelling in resistance athletes is appealing. An increase in relative wall thickness would dissipate the high wall stress hypothesised to occur during heavy resistance exercise. However, as outlined above (Chapter 2.3.2), exercise accompanied with a Valsalva manoevure normalises transmural wall stress. Therefore, it is unsurprising, perhaps, that several cross-sectional and longitiudinal studies have reported that resistance training was not associated with substantial differences in LV wall thickness, cavity size or mass, in young, middle-aged or older men and women (Haykowsky *et al.*, 2000*c*, 2000*b*, 2000*a*, 2005). Three meta-analyses have been conducted within the last 25 years which examined sport-specific structural remodelling, each demonstrating an absence of *absolute* dichotomous remodelling between endurance and resistance athletes (Fagard, 1996; Pluim *et al.*, 2000; Utomi *et al.*, 2013). Nonetheless, resistance training has frequently been associated with a predominant concentric remodelling, demonstrated by an increase in both absolute wall thickness and wall thickness relative to internal chamber dimension (Pluim *et al.*, 2000). Longitudinal studies specifically assessing the influence of resistance training interventions also remain conflicted. Baggish et al. (2008*a*) demonstrated a concentric remodelling pattern (increase in LV mass and wall thickness without change in chamber volume) in 24 football players before and after 90 days of training intensification. This finding was further supported in a follow-up study by the same

group, which identified an increased risk of hypertension, arterial stiffness and reduced LV diastolic function among 126 collegiate American football athletes who develop concentric remodelling (Kim *et al.*, 2019). However, in 13 untrained individuals whom underwent 6 months of resistance training, Spence et al. (2011) did not find evidence of structural cardiac adaptation using MRI, the gold standard technique for the assessment of ventricular structure (Gerche *et al.*, 2013; Petersen *et al.*, 2017). As such, the concentric type remodelling proposed by Morganroth, has received much scrutiny and contradiction (Naylor *et al.*, 2008; Utomi *et al.*, 2013; Haykowsky *et al.*, 2018; Kindermann *et al.*, 2019). Similar to the phasic remodelling pattern suggested for LV remodelling following endurance training, it is plausible that a similar pattern is observed in response to resistance training. Again, in the study by Spence et al. (2011), participants were randomly assigned to either 6 months of endurance or resistance training. Competitive American football players recruited by Baggish et al. (2008*a*), however, would have had a substantial training history prior to the 90 day training intensification. It is possible that prior long-term training encourages a phenotypic plasticity towards concentric remodelling, allowing tissue to accommodate specific demands from previous exposure, similar to that which has been suggested in the skeletal muscles of athletes (Flück *et al.*, 2019). Additionally, American-football may be described as a 'mixed' sport (Mitchell *et al.*, 1994), generating both pressure and volume loads (i.e., combined increase in aortic blood pressure and cardiac output) (Naylor *et al.*, 2008) and therefore a different haemodynamic load compared with strict resistance-type exercise (i.e., increase in aortic blood pressure, with small increase in cardiac output). Furthermore, American football is often played in hot environments with protective clothing, resulting in adaptations to heat stress such as plasma volume expansion (Godek *et al.*, 2005), which can have profound effects on ventricular filling and preload (Périard *et al.*, 2016), thereby acting an additional stimulus for remodelling.

One reason for equivocal findings between studies assessing the resistance-athletes heart may relate to the way in which, if any, parameters are scaled for differences in body size (Naylor *et al.*, 2008). The association between body size and cardiac structure is now well established (Batterham *et al.*, 1999; Dewey *et al.*, 2008), which is pertinent when evaluating resistance-trained athletes, whom typically demonstrate larger body size and proportion of fat free mass when compared with endurance athletes or non-athletic controls. As such, increased chamber dimensions and wall thicknesses previously reported in resistance athletes may simply reflect a larger body size; or at least cardiac parameters may be exaggerated when compared to smaller individuals. Indeed, previous observations suggest that body size accounts for up to 50% of the adult LV dimension variability (Pelliccia *et al.*, 1999). Furthermore, the type of scaling approach requires consideration. Ratiometric scaling of cardiovascular parameters, i.e., the parameter is simply divided by a measure of body size, is often inappropriate, since few parameters demonstrate a purely linear relationship (Tanner, 1949). Rather, most cardiovascular variables exhibit an exponential relationship with body size measurements, requiring allometric scaling using a scaling exponent (i.e., cardiovascular variable divided by body size measure, raised to a scalar exponent). Body surface area is the most common index of body size (Naylor *et al.*, 2008), although fat free mass has been shown to be the most ideal scaling variable (Batterham & George, 1998). Inappropriate, or absent, scaling measures may have perpetuated the Morganroth hypothesis relating to concentric remodelling of resistance-type athletes. Greater body size is likely to contribute towards a large proportion of the differences observed in LV structure between resistance athletes and non-athletes. In support of this, numerous studies have demonstrated that differences in absolute LV mass between resistance athletes and controls are reduced or removed, when appropriately indexed (Longhurst & Stebbins, 1997; Lalande & Baldi, 2007; Naylor *et al.*, 2008). Blood volume, on the other hand, appears to scale ratiometricaly with body mass, and hence

provides a justification for scaling intravenous infusions to body mass (Stahl, 1967; Prothero, 1980; Bengtsson & Edén, 2003).

Confounding influences, including the use of anabolic steroids, may contribute to the conflict and debate surrounding the presence and magnitude of structural remodelling in resistance-trained athletes. Indeed, (Urhausen & Kindermann, 1999) and Luijkx, Velthuis, Backx, Buckens, Prakken, Rienks, Mali and Cramer (Luijkx *et al.*, 2013) did not observe concentric LV hypertrophy in athletes abstaining from anabolic steroids. In addition, diastolic and systolic function were reduced, and relative wall thickness was greater in resistance athletes using performance enhancing substances compared to non-using athletes (Baggish *et al.*, 2017). Moreover, LV wall thickness has been evidenced to correlate with the extent of anabolic steroid misuse (Urhausen *et al.*, 2004). Lack of consistent concentric-type hypertrophy in resistance-trained athletes may also be due to the diverse haemodynamic load elicited by different types of resistance training, i.e., limited exposure to an increased haemodynamic afterload since an increase in blood pressure only occurs sporadically due to the intermittent nature of repetitions and work-to-rest ratios. Given that resistance trained athletes from diverse sporting disciplines vary with respect to the type of exercises performed, training dose (i.e., weight lifted, number of sets and repetitions, training sessions per week), duration of rest, and caloric intake, analagous to skeletal muscle, it is likely that cardiac remodelling may not be homogeneous. Indeed, the heterogeneous remodelling pattern was highlighted in a systematic review, finding that normal geometry was most common in powerlifters, whilst concentric hypetrophy most common in weightlifters and eccentric hypertrophy most common in bodybuilders (Haykowsky *et al.*, 2002). It is plausible that the haemodynamic volume and pressure loads differ across these different cohorts of 'resistance athletes'. Body builders, for example, may have a greater volume load than power lifters during submaximal and maximal lower extremity exercise, as demonstrated by significantly higher stroke volume and cardiac

output response in comparison to powerlifters (Falkel *et al.*, 1992). This is also consistent with Pelliccia et al. (1993) who found bodybuilders have greater LV cavity dimensions compared with powerlifters and Olympic weightlifters. Clearly, the training aims between these different types of resistance athletes differ. Powerlifting, for example, aims to increase maximal strength, specifically in movements such as the squat, bench press and deadlift whilst body building aims to optimise muscle hypertrophy whilst reducing body fat (Kraemer & Ratamess, 2004). As such, body builders typically train with high training volume, and short rest periods whilst power lifters typically train with low-to-moderate training volume and longer rest periods between bouts of highly explosive movements (Kraemer & Ratamess, 2004). Perhaps also important is the respiratory modulation of venous return and the utilisation of the Valsalva, which may mitigate any potential increase in transmural wall stress (Chapter 2.5.1). It may also be important to consider influence of prior training engagement during childhood and adolescence, and whether programming during this period of developmental plasticity elicts any long-term adaptation (Asif *et al.*, 2018; Perkins *et al.*, 2018). For example, exercise training in juvenile rats led to sustained cardiac remodelling, including increased LV mass, wall thicknenning and cardiomyocyte number, which persisted to adulthood (Asif *et al.*, 2018). Furthermore, in this study, the remodelling in the juvenile exercise group (training 5-9 weeks of life) surpassed that of the adult rats who completed the same exercise program (at 20-24 weeks of life). Similar findings demonstrating a potentail long-lasting adaptation to exercise during maturation have also been shown for other systems of the mammalian body, such as the neural development of the brain (Shevtsova *et al.*, 2017) and pancreatic B cell mass in growth restricted rats (Laker *et al.*, 2011). Taken together these rodent studies suggest that early-life exercise training can provide long-term adaptation, although whether these exercise-induced programming effects exist in humans are yet to be ascertained. In summary, contrasting the original Morganroth hypothesis, data supporting concentric remodelling

following resistance training remains equivocal. Appropriate scaling of structural cardiac parameters to body composition often removes differences between groups and confounding factors such as anabolic steroid use may, at least partly, explain observational findings of a concentric LV remodelling pattern in resistance athletes, although long-term training history may also be an important consideration.

2.6.2.3 Resting left ventricular function in the resistance athlete's heart

Although conventional echocardiographic and MRI, have often failed to differentiate remodelling of endurance vs resistance athlete's heart, indices of function appear to show a different pattern. While global radial strain was similar, global circumferential strain was lower in bodybuilders (Szauder *et al.*, 2015) and global longitudinal strain was lower in runners. Circumferential strain in body builders was also closely related to LV mass (r = 0.61; P < 0.01). Furthermore, twist mechanics are increased in athletes engaged in high-static, low-dynamic sports, mediated predominantly by an increase in apical rotation (Santoro *et al.*, 2014). It is speculated that elevated rotation at rest may become a compensatory mechanism to overcome increasing aortic pressure during sport-specific resistance exercise (Beaumont *et al.*, 2017*a*). Experimental studies, for example, have demonstrated an impaired twist (via a reduction in apical rotation) in response to isometric handgrip exercise designed to increase LV afterload (Weiner *et al.*, 2012; Balmain *et al.*, 2016). Conversely, in a longitudinal study involving strength (American football) athletes, Baggish et al. (2008*a*) demonstrated that participation in 90 days of training-intensification, diastolic function (assessed as tissue Doppler early diastolic velocity; E') declined in strength athletes, with increasing LV mass and wall thickness but no change in LV volume (i.e., concentric hypertrophy). Whilst concerns may be raised over the athletic population used and potential confounding influences such as ethnicity, hypertension, and exposure to performance enhancing supplements, it is interesting that diastolic function appears to be reduced (Baggish *et al.*, 2008*a*). It is plausible that these findings may be related to a

reduction in LV compliance (Mihl *et al.*, 2008). Resistance training has also been shown to have a deleterious effect on systemic arterial compliance (Otsuki *et al.*, 2007; Babaee Bigi & Aslani, 2007) and measures of arterial stiffness in highly-trained athletes (Kasikcioglu *et al.*, 2004; D'Andrea *et al.*, 2012; Kim *et al.*, 2015). Indeed, small but significant elevations in resting blood pressure may be partly responsible for the observed LV concentric remodelling in resistance athletes, owing to the chronic haemodynamic pressure stress.

In summary, it is possible that resistance training has the capacity to alter the structure and function of the LV and systemic vasculature. It is possible, however, that the 'threshold' for remodelling is not always attained due to the diverse haemodynamic load elicited by different types and volumes of resistance training, hence leading to an abundance of equivocal findings. Both animal (Leite-Moreira *et al.*, 1999) and human studies (Weiner *et al.*, 2012) have demonstrated the detrimental effect of transient increases in systolic pressure on LV function; it is not currently known whether or not structural and/or functional remodelling associated with resistance exercise training results in a preferential adaptation to preserve LV function during acute surges in blood pressure (i.e., preserving SV).

2.6.3 Right Ventricular Remodelling with Resistance Training

RV wall stress is unlikely to be altered during resistance exercise (Chapter 2.3.3), and so it is unsurprising that no association between RV remodelling and resistance training has been revealed. However, relatively few studies have assessed the long-term impact of resistance training on the RV. In a 3-month echocardiographic study, (Baggish *et al.*, 2008*a*) showed an absence of RV remodelling in 24 previously competitive collegiate American footballers. However, it may be argued that American football represents a mixed combination of both aerobic and resistive components (duManoir *et al.*, 2007). Nonetheless, one might expect the haemodynamic stimuli from mixed sports to be of the

greatest magnitude, owing to the additive pressure and volume load. Previously competitive rowers ($n = 40$) from the same study, for example, showed an increase in resting structural and functional RV measures post-training. In contrast, using gold standard cardiac MRI techniques to assess RV structure, Spence et al. (2013*a*) demonstrated a similar, although smaller magnitude of RV remodelling pattern in previously non-trained resistance-trained ($n = 10$) vs. endurance-trained ($n = 13$) participants following six months of sport-specific training. In comparison to the former study, Spence et al. (2013*a*) applied specific exercise interventions over a 6 month clearly differentiating endurance training from resistance training (high dynamic vs. high static component, respectively). The disparity between the magnitude of LV and RV remodelling may be explained, in part, by the type of resistance exercise performed, since brief, intermittent activity may not place a sufficient haemodynamic load on the heart, particularly on the RV (Naylor *et al.*, 2008; Spence *et al.*, 2013*b*), as discussed in Chapter 2.5.2. An increase in cardiac output may be required in order to elicit RV remodelling with resistance training. An absence of "volume" load in this context will not alter chamber dimensions or influence downstream pulmonary artery pressure, which is proportional to cardiac output (La Gerche *et al.*, 2010), and remodelling of the RV might be predominantly reserved for endurance-based dynamic activity. However, few studies have considered the influence of resistance training on remodelling of the right heart. Nonetheless, rigorous characterisation of RV structure and function in resistance trained athletes is an important area of future work. As suggested by an important review in this area, future studies should employ advanced imaging modalities (i.e., gold standard MRI), with longitudinal within-subject designs, and ensure that appropriate scaling techniques are employed and rigorous description of training history is made (Naylor *et al.*, 2008).

2.7 Cardiac Functional Adaptation: Functional Response to Haemodynamic Perturbation

2.7.1 Left Ventricular Response to Haemodynamic Perturbation in the Remodelled Heart

Analogous to skeletal muscle (van Wessel *et al.*, 2010), the repetitive exposure to specific stimuli (i.e., pressure or volume) may cause a training-specific adaptation in the functional response to a haemodynamic challenge. As recently proposed by (Shave *et al.*, 2019), it is possible that the divergent haemodynamic stimuli associated with chronic endurance and resistance training promotes differential cardiac adaptations that compromise the heart's ability to accommodate pressure and volume, respectively. Following 90 days of intensive endurance or resistance training, Shave et al. (2019) observed a relative trade-off in the training-specific capacity to respond to a haemodynamic volume or pressure challenge, represented by a saline infusion and isometric handgrip challenge, respectively. Endurance athletes, who demonstrated eccentric remodelling, increased LV SV (16%) in response to rapid intravenous saline infusion but were unable to preserve SV when challenged with isometric hand grip exercise (-21%). Resistance athletes, in contrast, developed a concentric LV remodelling phenotype (i.e., increased relative wall thickness) and were less capable of increasing SV during saline infusion (6%) but demonstrated an enhanced capacity to maintain SV when pressure challenged (-4%; **Figure 10**). As such, it was proposed that LV remodelling associated with endurance or resistance exercise conveys a training-specific functional response to preload and afterload, respectively. This may compromise the athlete's ability to respond to the abrupt increases in pressure or volume, in endurance and resistance athletes, respectively. However, as discussed in Chapter 2.4.2, concentric remodelling is not always associated with resistance training. Furthermore, as transmural LV wall stress is not elevated during resistance exercise when accompanied by a Valsalva manoeuvre, the stimulus for LV structural and functional adaptation may be

absent. Haykowsky et al. (2001) provides support of this using a cohort of resistance-trained men only. Yet, prior non-invasive assessment of LV wall stress during isometric handgrip exercise (not accompanied by a Valsalva manoeuvre) has indicated that there may in fact be a training-specific functional response which mitigates an increase in LV wall stress. Galanti et al. (1992) demonstrated that LV end-systolic wall stress was not altered in resistance athletes but increased by 28% in sedentary individuals, despite a similar increase in systolic blood pressure in both groups. Athletes were able to decrease end-systolic cavity area, which effectively counteracted the influence of increasing systolic blood pressure on LV wall stress. Therefore, transient alterations in LV geometry may minimise LV transmural wall stress in resistance-trained athletes during static exercise, which may not exist in untrained counterparts and supports the proposed hypothesis of LV functional remodelling following resistance trianing.
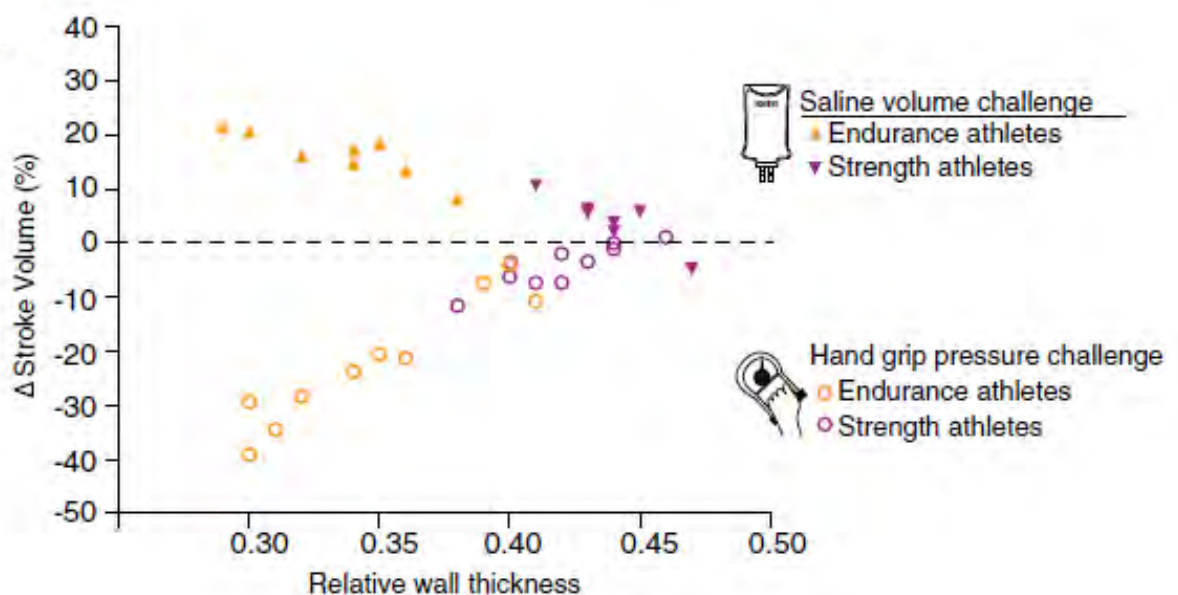
Figure 10. Relationship between relative wall thickness and LV SV in response to rapid intravascular saline infusion (triangles) and isometric hand grip exercise (circles) in endurance athletes (orange) and strength athletes) purple.

Adapted from Shave et al. (2019).

Contrary to prior assertion, Wasfy et al. (2019) evidence that eccentric remodelling does not come at the expense of an ability to handle acute surges in pressure. Following 90 days of swimming training intensification, no reduction was observed in LV SV during isometric handgrip exercise, and the response was similar between the swimmers and untrained individuals. However, as athletes showed a greater impairment in LV twist mechanics after training intensification, SV preservation was likely mediated by a compensatory increase in diastolic function (as evidenced by enhanced myocardial velocities during diastole and a faster untwisting rate). Whilst the findings from this study warrants validation and further directed study, it presents an interesting paradigm by which to assess the athlete's heart. Both Wasfy et al. (2019) and Shave et al. (2019) utilised isometric handgrip to generate a pressure stimulus, however engaging the larger muscles of the lower body, as performed by Haykowsky et al (2001), may be more ecologically relevant to the training stimulus for most able-bodied sports. Furthermore, the amount of muscle mass activated directly influences the magnitude of the exercise pressor response (MacDougall *et al.*, 1985).

2.7.2 Right Ventricular Response to Haemodynamic Perturbation in the Remodelled Heart

Differences in RV structure and function at rest are unlikely to reflect the full extent of cardiac remodelling. At rest, the work requirement of the RV is minimal because of the low RV afterload, whereas loading conditions may increase dramatically during intense dynamic exercise (La Gerche *et al.*, 2011). Although few studies have assessed RV wall mechanics during exercise, a normal contractile reserve has been observed in healthy athletes (La Gerche *et al.*, 2012*a*; Sanz-de la Garza *et al.*, 2017*a*; Claeys *et al.*, 2020), which may help to identify those with underlying abnormalities such as arrhythmogenic right ventricular cardiomyopathy (Claeys *et al.*, 2020). Despite cross-sectional observations of altered regional RV function in athletes, only one study has reported regional measures

during exercise (Sanz-de la Garza *et al.*, 2017*a*). In this study, whilst the increase in basal longitudinal strain was similar between athletes and untrained controls, the change in apical strain was significantly lower in athletes. It is possible that endurance athletes develop a region-specific functional response to haemodynamic perturbation, which differentially affects myocardial wall mechanics at the dilated basal region, in comparison to the highly trabeculated apex. An increased reliance on longitudinal deformation at the base of the RV may facilitate greater SV generation, since the basal section contributes most to overall RV volume (Bodhey *et al.*, 2008). Further assessment of the functional RV response to haemodynamic perturbation is crucial to improving our understanding of normal physiological remodelling of the RV.

2.8 General Summary of Literature Review

This chapter has provided an overview of the fundamental anatomy and physiology of the heart, and the acute response and chronic remodelling process to endurance and resistance exercise training. Despite recent acknowledgement of the considerable haemodynamic load that the RV is exposed to during endurance-type exercise, and the associated remodelling of RV structure, comprehensive assessment of RV function among such athletes remains unanswered. Conversely, remodelling of the LV has been well studied in both endurance- and resistance-trained athletes, at rest. Arguably more important than the assessment of resting structure and function, however, is the functional ventricular response to haemodynamic load, such as that which occurs with exercise. Given the divergent haemodynamic load on the LV elicited by resistance exercise and endurance exercise, it is plausible that the functional response to specific haemodynamic stimuli (i.e., pressure or volume) are also different. The subsequent experimental chapters of this thesis will address these gaps within the scientific literature, which warrant further investigation to further our understanding of normal physiologic cardiac adaptation to exercise.

2.9 Thesis Aims

The aim of this thesis is to examine right and left ventricular function in athletes, and to examine the functional response to specific haemodynamic stimuli. Three studies were completed to address the following aims. Hypotheses are presented in the introduction to each experimental chapter.

2.9.1 Chapter 4. Right Ventricular Function and Region-Specific Adaptation in Athletes Engaged in High-Dynamic Sports: A Meta-Analysis

Aims: To examine and compare RVSP and RV free-wall and regional systolic function in endurance athletes in comparison to non-athletic controls, using previously published data.

2.9.2 Chapter 5. Evidence of Region-Specific Right Ventricular Functional Remodelling in Endurance-Trained Men in Response to Acute Volume Infusion

*Aim*s: To examine and compare the global and regional RV response to acute haemodynamic volume load in endurance athletes and non-athletic controls.

2.9.3 Chapter 6. Stimulus-Specific Functional Remodelling of the Left Ventricle in Endurance and Resistance-Trained Men

Aims: To compare the LV response of endurance-and resistance-trained men and non-athletic controls to i) an acute haemodynamic pressure load and ii) an haemodynamic volume load. A secondary aim of this study was to investigate the mechanisms responsible for potential training-specific functional remodelling, by examining LV longitudinal myocardial deformation characteristics in the three groups.

Chapter 3

General Experimental Methods

Chapter 3. General Experimental Methods

3.1 Introduction

This chapter describes the general methods of data collection and analysis that are applicable to Chapter 5 and Chapter 6. Methods specific to individual studies that are not outlined in the general methods are provided in more detail in the respective chapters.

3.2 Ethical Approval

Due to the nature of data collection, ethical approval was obtained from the Cardiff School of Sport and Health Sciences Research Ethics Committee prior to data collection for each study (**Appendix V** and **Appendix VII**). All experimental procedures conformed to the *1975 Declaration of Helsinki*, with the exception of being registered as a trial.

3.3 Thesis Study Design

In Chapter 4, a meta-analysis was conducted to compare RV systolic function in high-dynamic athletes (i.e., regular contraction of large muscle groups and sustained increase in oxygen consumption, according to the Mitchell Categorisation) vs. non-athletic controls, with specific consideration of regional adaptation. The methodology associated with this chapter is described in detail in Chapter 4. In Chapters 5 and 6, a cross-sectional study design was employed to assess exercise-induced functional remodelling of the heart to acute haemodynamic perturbation. A schematic detailing the experimental chapters is provided in **Figure 11**. As such, endurance-trained and resistance-trained individuals were recruited, together with a group of non-athletic control counterparts. The first testing session involved the assessment of body mass and stature and resting blood pressure, prior to the assessment of a seated leg-press one-repetition maximum (1RM). After a 30-minute recovery, an incremental cycling test to exhaustion was completed to assess cardiorespiratory fitness. The subsequent experimental visit involved either a systemic pressure load or a volume load, with the final visit involving the alternate experimental condition.

	P Participants	**I** Intervention	**C** Comparison	**O** Outcome Variables	**S** Study Design	Search Strategy
Chapter 4 Meta-Analysis	Highly-trained endurance athletes	None	Non-athletic controls	RVSP rest/exercise TAPSE S' RV FWSL RV FWSR Regional RV FWSL	Cross-sectional or longitudinal design (> 2 years training volume > 6 hours/week)	PubMed MEDLINE Scopus Science Direct Web of Science
Chapter 5 & 6		Visit 1	Anthropometry	Maximal Leg Press	30 min rest	Maximal Cycling Test
		Visit 2 Experimental Pressure Load	Echocardiography — LV Baseline	Leg press exercise at 20%, 40% and 60% of 1RM		
		Visit 3 Experimental Volume Load	RV LV Baseline	7.5 ml/kg Infusion	Passive leg-raise	

Figure 11. Thesis schematic.

Chapter 4 collated published data reporting measures of RV function in both endurance athletes and non-athletic controls. Articles were assessed for eligibility using the PICOS (participants, interventions, comparisons, outcomes and study design) framework. Chapter 5 and 6 consists data that was captured during the same period of data collection, with two distinct questions. The first visit included assessments of anthropometrics and peripheral blood pressure, followed by the assessment of one-repetition maximum during leg press exercise. After 30 minutes of recovery, an incremental maximal exercise test was conducted on a cycle ergometer to assess cardiorespiratory fitness. The subsequent experimental visit consisted either an experimental pressure load on the LV, achieved via incremental leg-press exercise, or a 7 ml/kg intravenous Gelofusine infusion. In line with the study aims. echocardiography of the LV was performed during both visits, whilst images of the RV were captured during the volume infusion visit only.

3.4 Experimental Study (Chapter 5 and 6)

3.4.1 Participant Recruitment

Participants were recruited on a voluntary basis and provided written informed consent after having been informed of the rationale, purpose and procedures involved in the testing protocol. Participants were informed of the risks and their right to withdraw from the study at any point. Research members responsible for providing this information and collecting informed consent received training ("Process of Taking Consent"). All participants completed a health questionnaire and participant activity readiness questionnaire (PARQ+) prior to undertaking any test procedures.

3.4.2 Participants

Non-elite but highly-trained (athletes engaged with dedicated, structured training programmes, participating in four or more training sessions per week, having done so for 2 or more years) i) endurance-trained ($n = 2$ cyclists, $n = 5$ triathletes and $n = 8$ long-distance runners) and ii) resistance-trained individuals ($n = 2$ natural body builders, $n = 5$ weight lifters and $n = 7$ non-specific resistance athletes (i.e., gym goers)) and iii) nonathletic controls (performing no more than two forms of brief moderate physical activity per week, and not meeting the UK and world health organisation physical activity guidelines (Bull *et al.*, 2020) were recruited for the experimental procedures in Chapter 5 and Chapter 6. Endurance athletes were defined as those with a training history that clearly reflected prolonged but intermittent periods of dynamic exercise involving continuous effort (Oxborough *et al.*, 2012*b*). For the purpose of this thesis, resistance athletes were defined as those engaged in the progressive use of resistive loads to increase one's ability to exert and resist force (Myers *et al.*, 2017). Participants were aged between 18 and 45 years of age and reported to be free from cardiovascular, respiratory and metabolic disease and without early family history of cardiovascular disease. Exclusion criteria also included:

females, history of atopy (tendency to develop allergic diseases), blood pressure over 140 mmHg systolic and 90 mmHg diastolic, smokers and the use of cardioactive drugs and prescribed medications. Due to the experimental procedures involving intravenous volume infusion, competitive athletes subject to doping regulations were also unable to be recruited; Gelofusine is listed as a banned substance by the UK and world anti-doping agencies, as it can act as a potential masking agent. Participants were recruited from Cardiff Metropolitan University and local running, cycling, triathlon, and weightlifting clubs and gyms.

3.4.3 Experimental Conditions

All participants were asked to complete three experimental visits in a temperature-controlled laboratory (temperature range, 21-23°C). All experimental testing was performed in the Cardiff School of Sport and Health Sciences Physiology Laboratory. Participants were asked to refrain from caffeine 12 hours preceding experimental procedures, and alcohol and vigorous exercise 24 hours prior to their visit.

3.4.3.1 Experimental Pressure Load

Isometric leg-press exercise at 20%, 40% and 60% of one-repetition maximum (1RM) was used to elicit progressive increases in systemic blood pressure, as has been shown previously (Haykowsky *et al.*, 2001; Stohr *et al.*, 2017). Baseline echocardiographic measurements were obtained with the participant seated on the leg-press machine with legs elevated, and feet positioned on the weight-bearing platform. Blood pressure was acquired continuously using finger plethysmography (Finometer PRO; Finapres Medical Systems FMS, Arnhem, The Netherlands) and was calibrated to manual blood pressure obtained at baseline. A blood pressure cuff was carefully attached to the second or third digit of the right hand Beat-by-beat arterial blood pressure monitoring was achieved via photo-electric plethysmography, utilising the vascular unloading technique of Peňáz (1973) and the

Physiocal criteria of Wesseling (1995). Briefly, the infrared light is absorbed by the blood, and the pulsation of arterial diameter during systole causes a pulsation in the light detector signal, which is transformed into a pressure waveform. The hydrostatic height correction unit of the Finometer was kept near heart level. Brachial artery pressure is reconstructed from finger arterial pressure real time using a transfer function (involving waveform filtering, and level correction) (Gizdulich & Wesseling, 1990; Gizdulich *et al.*, 1997; Guelen *et al.*, 2008). A return to flow calibration was used to ensure accuracy of blood pressure measurements, via automated sphygmomanometry, wherein an arm cuff is placed around the same arm as the finger cuff, and inflated until suprasystolic, then deflated until the finger cuff detects a return of flow. The arm cuff pressure is read at that instant, and reconstructed brachial pressure is corrected to this value. These data were sampled at 1000 Hz using a commercial data acquisition system and stored for offline data analysis (Chart Version 8, Lab Chart Pro, AD Instruments, UK). The reconstructed brachial artery pressure waveform was calibrated at baseline to a resting manual blood pressure recording (Welch Allyn Durashock DS66, UK). Data were analysed in 30 second bins, which were aligned to the start of echocardiographic image acquisition. The accuracy and precision of reconstructed brachial pressures from finger pressure by the Finometer has been demonstrated to be comparable to intra-arterial brachial pressure with an accuracy of less than 5 mm Hg and a precision of less than 8 mm Hg and an excellent correlation (r = 0.94) between reconstructed and measured intraarterial pressures (Bos *et al.*, 1996; Imholz *et al.*, 1998; Guelen *et al.*, 2008)

Individuals were then instructed to push against the weight-bearing platform, maintaining a knee joint angle of 120° for two-minutes. Transthoracic echocardiography was performed between the first and second minute of isometric exercise; individuals were instructed to refrain from performing a Valsalva manoeuvre throughout each repetition. This protocol

was repeated for progressive loads corresponding to 20%, 40% and 60% of 1RM, with a two-minute recovery between each effort.

3.4.3.2 Experimental Volume Load

During the volume-loading condition, echocardiography measurements were obtained, in the lateral decubitus position, before and immediately after intravenous Gelofusine infusion (succinylated gelatin 4%; 7 ml·kg^{-1}) infused over a 30-minute period, and again following 2-minutes passive leg elevation at a hip flexion angle of 45°. Gelofusine was specifically chosen as the infusion substance, instead of saline, as it is maintained in the intravascular space for longer, therefore causing a larger and more consistent volume challenge (Lobo *et al.*, 2010).

Chapter 6 (***Stimulus-specific functional remodelling of the left ventricle in endurance and resistance-trained men***) utilised data obtained from each experimental visit. However, as discussed in Chapter 2.3.3, there is no evidence to suggest the RV is haemodynamically challenged during resistance-type exercise and structural remodelling of the RV following long-term resistance training has not previously been observed. As such, resistance-trained individuals and the experimental systemic pressure-loading stimulus were not included in the specific analysis concerning Chapter 5 (***Region-specific right ventricular functional remodelling in endurance-trained men in response to acute volume infusion***).

3.5 Data Acquisition

3.5.1 Anthropometry

Stature was assessed using a wall-mounted stadiometer (Holtain, Fixed Stadiometer, Pembs, UK), and recorded to the nearest 0.1 cm. Body mass was recorded using electronic scales (SECA, Model 770, Vogel & Halke, Hamburg, Germany), and recorded to the

nearest 0.1 kg. From these data, body mass index (BMI; BMI = body mass / stature^2) and body surface area (BSA; BSA = 0.20247 * height (m)$^{0.725}$ * body mass (kg)$^{0.425}$) were calculated (Du Bois & Du Bois, 1989).

3.5.2 Leg-Press - One-Repetition Maximum

Resistance exercise was performed on a commercially available leg-press machine (Linear Leg Press, Life Fitness Ltd, Queen Adelaide, UK). The 1RM protocol for the 45° inclined double leg-press was determined according to the National Strength and Conditioning Association guidelines (Earle, 2008). Participants initially completed a 5 to 10 repetition warm-up against light resistance. After a 2-minute rest period, the first attempt was performed using a load that was ~50% of the participants' weight-predicted 1RM. Following a 3-5-minute rest, participants repeated the exercise with an increased load. This process was repeated until participants could only perform a single repetition and required between 3 and 5 attempts to achieve the correct load.

3.5.3 Cardiorespiratory Fitness

All participants completed an upright incremental exercise test to exhaustion on an electronically gated cycle ergometer (Lode Corival, Groningen, The Netherlands). Exercise was started at 50 Watts for both the resistance-trained individuals and controls, and at 120 watts for the endurance-trained individuals. Exercise load was incrementally increased by 20 watts every minute until volitional exhaustion. Measurements of ventilatory gas exchange were obtained using a mask-based, breath-by-breath gas analysis system (Jaeger, Oxycon Pro, Warwickshire, UK). Peak oxygen uptake was defined as the highest $\dot{V}O_2$ averaged over a 30-s consecutive period. Heart rate was measured throughout the exercise test via a telemetry-based chest strap, providing continuous heart rate monitoring (Polar Electro, RS400, Finland).

3.5.4 Haemodynamics

Supine brachial arterial blood pressure was determined, in triplicate, for all participants via manual sphygmomanometry (Welch Allyn Durashock DS66, UK). A stethoscope (Littmann Classic, Littman, 3M Bracknell, UK) was placed on the arm, distal to the cuff, in the antecubital space and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were determined using manual auscultation. Manual blood pressures obtained at rest were used to calibrate blood pressure obtained continuously using finger plethysmography (Finometer PRO; Finapres Medical Systems FMS, Arnhem, The Netherlands). A 3 cable ECG (Lead II configuration) recorded heart rate throughout echocardiographic imaging.

3.5.5 Blood Volume

Changes in blood volume (BV) were calculated according to (Dill & Costill, 1974), utilizing haemoglobin (Hb) concentration and assuming blood volume pre-infusion was 100%, using the following equation:

$$BV_{post} = BV_{pre} (Hb_{pre}/Hb_{post})$$

$$\Delta BV (\%) = 100 (BV_{post} - BV_{pre}) / BV_{pre}$$

Venous blood was sampled before, mid-way and post-infusion and analysed for sodium (assessment termination criteria: < 133 mmol·l^{-1}), potassium (assessment termination criteria: < 3.5 mmol·l^{-1}), haemoglobin concentration, and haematocrit (assessment termination criteria: $< 40\%$) using a handheld point of care device (i-STAT1, i-STAT System, Abbott Point of Care, Princeton, New Jersey).

3.6 Echocardiography

Echocardiography is a non-invasive technique that uses ultrasound technology (i.e. high frequency sound) to produce images of the anatomy of the heart. A detailed explanation of the principles and physics of echocardiography is beyond the scope of this thesis but has

been covered in detail previously (Armstrong *et al.*, 2010). Briefly, vibration of piezoelectrical crystals located in the handheld transducer generates an ultrasound pulse that is transmitted into the body and absorbed by the tissues. The proportion of ultrasound that is not absorbed is reflected back to the transducer. Image formation is based upon the time interval between ultrasound transmission and arrival of the reflected signal. Various echocardiographic modalities differ in the way that the reflected sound is collected and analysed. A description of the modalities used within this thesis are presented below. Further detail of specific parameters used to address the research questions of study 2 and study 3 are provided in Chapter 5 and Chapter 6.

3.6.1 2D Imaging and M-Mode

Ultrasound pulses are transmitted along a series of lines spanning across an imaging plane. Each pulsed ultrasound creates one scan line, and when collated, form a frame. A sequence of frames repeated over time provide a real-time moving two-dimensional (2D) image of the heart. 2D imaging is used to assess the orientation and anatomical structure of the heart, including RV and LV volumes and dimensions.

From a 2D image, assessment of a single pulsed ultrasound scan line can be displayed using the motion mode (M-mode) modality. M Mode records depth and motion of echoes with a high frame rate and therefore provides detailed information on fast moving cardiac structures. M Mode echocardiography was used to measure the longitudinal motion of the tricuspid annulus (tricuspid annular plane systolic excursion; TAPSE), as a measure of RV systolic function.

3.6.2 Spectral Doppler

Blood flow can be assessed indirectly via echocardiography, using the pulsed-wave and continuous wave Doppler ultrasound. The Doppler principle is based on the frequency shift that occurs between transmitted and reflected ultrasound. If blood cells are moving towards

the transducer when the ultrasound is reflected, then the returned wavelength will be shortened producing an increase in frequency. Equally, blood cells moving away from the transducer will lengthen the wavelength, decreasing frequency (Armstrong *et al.*, 2010). In this thesis, continuous wave Doppler was aligned over the tricuspid valve to quantify the peak tricuspid regurgitant jet velocity. Using the simplified Bernoulli equation ($4*Velocity^2$), the pressure gradient between the RA and the RV can be quantified. Addition of RA pressure, therefore, provides a reliable estimation of RVSP (Rudski *et al.*, 2010). In the absence of a pressure gradient across the pulmonic valve or RVOT, RVSP is equal to PASP due to an equilibration of pressures between the RV and PA during systole with the pulmonary valve open. Because velocity measurements are angle dependent, TR signals were obtained from a modified apical four chamber, parasternal long axis view of the RV inflow, and the parasternal short axis view of the basal RV (**Figure 12**). The window providing the highest velocity signal was used and, for consistency, subsequent measurements were taken from the same imaging window within each participant. The determination of PASP by the sum of the peak RV-RA gradient and RA pressure (as outlined), has been established as a reliable method since 1984 (Yock & Popp, 1984). The use of PASP has been validated by other studies utilising simultaneous RV catheterisation and continuous Doppler derived determination of pressure (Currie *et al.*, 1985; Janda *et al.*, 2011). Whilst right heart catheterisation is considered gold standard for the determination of ventricular pressure, utilisation of such techniques in healthy athletes is limited to only a few specialist centres (Bevegård *et al.*, 1963; Claessen *et al.*, 2016; Buchan *et al.*, 2019).
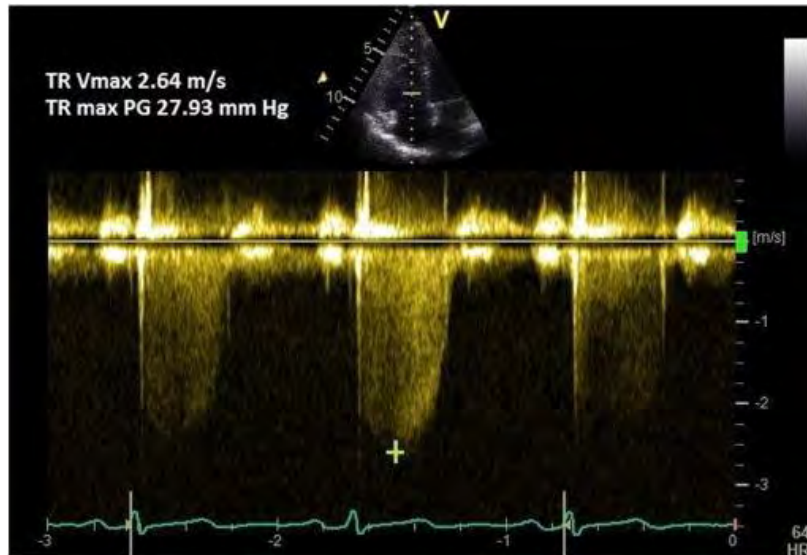
Figure 12. Tricuspid regurgitant velocity for the estimation of PASP.

Diastolic filling of the LV and RV was examined using pulsed-wave Doppler interrogation of mitral valve and tricuspid valve inflow velocities, respectively. From an apical four chamber view, the sample volume cursor was placed parallel to the flow at the level of the mitral of tricuspid annulus. Doppler velocity curves were digitised to obtain peak early filling velocity (E wave), peak late filling velocity (A wave), and calculation of early to late diastolic filling ratio (E/A) for both the LV and the RV (**Figure 13**).
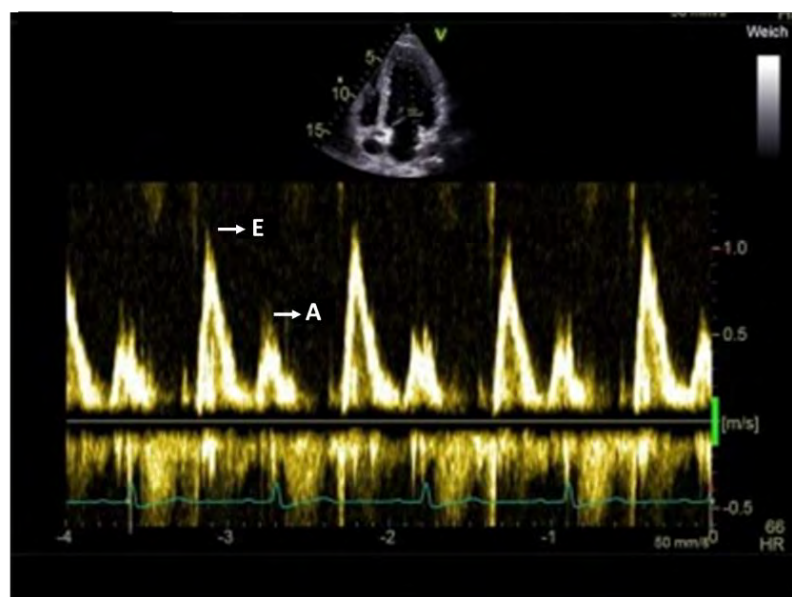
Figure 13. Doppler velocity curves of mitral valve inflow.

Peak early filling (E) and late filling (A) are identified.

3.6.3 Tissue Doppler

Tissue Doppler imaging utilises Doppler derived information to measure myocardial wall motion velocities. By placing the sample volume onto a region of interest, pulsed wave tissue Doppler imaging measures directional peak myocardial velocities. The myocardium, which reflects low velocity and very high amplitude Doppler signals, can be differentiated from blood cells that reflect low amplitude Doppler signals at a relatively high frequency. Tissue Doppler imaging was employed to assess both systolic and diastolic function of the LV and RV. From an apical 4-chamber view, the LV region of interest was placed at the level of the mitral annulus on the lateral wall and septal wall. For the RV, the region of interest was placed at the level of the tricuspid annulus on the lateral free wall. The peak velocity of the systolic myocardial wave (S'), early diastolic myocardial wave (E') and late diastolic myocardial wave (A') were quantified for each segment.

3.6.4 Speckle Tracking Echocardiography (Post-Processing)

2D speckle tracking echocardiography (STE) permits the calculation of angle independent myocardial deformation parameters such as strain and strain rate. Bright speckles in the ventricular wall are tracked throughout the cycle, creating natural acoustic markers for tagging the myocardial motion during the cardiac cycle (Blessberger & Binder, 2010). Post-processing with specialist software (GE Echopac), can identify the speckles and track them frame-by-frame during the cardiac cycle. Deformation is calculated using the Lagrangian method (Figure 14). Lagrangian strain is mathematically defined as the change of myocardial fibre length at end-systole compared to its original length at end-diastole (Pavlopoulos & Nihoyannopoulos, 2008), using the following equation:

$$\varepsilon_L(t) = \frac{[L(t) - L(t_0)]}{L(t_0)}$$

Where L(t) is the length of the object at time instance t following deformation and L. In more simple terms, strain is expressed as a fractional length change (**Figure 15**).
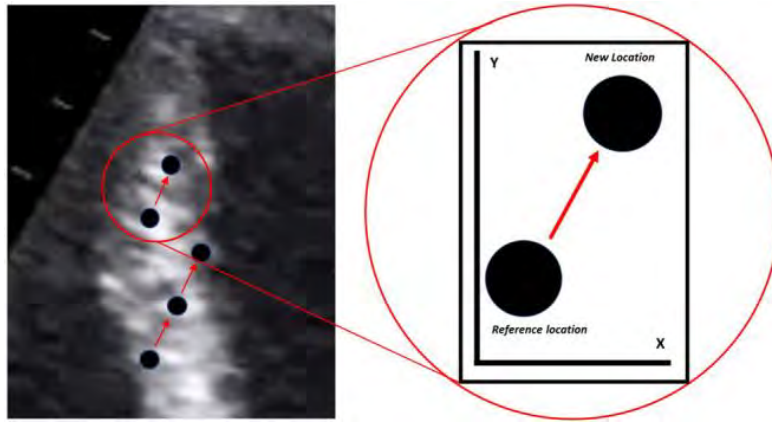
Figure 14. Theoretical concept of speckle tracking echocardiography.

Taken from Johnson et al. (2019).

Figure 15. Simple diagram showing the principle of Lagrangian strain.

Following deformation L(t) there is a change in length from initial reference L(t0) resulting in an increased length by delta L. Taken from Johnson et al. (2019).

LV longitudinal strain was measured from an apical four-chamber view at a frame rate between 60 and 90 frames per second, in accordance with previous guidance (Johnson *et al.*, 2019). A region of interest was manually traced along the endocardial border at the end of systole. Correct tracking of the myocardium was ensured by correct identification of the region of interest, and manual adjustment if necessary. After definition of the region of interest over the LV free-wall and septum, the post-processing software automatically divides the ventricle into six equally distributed segments (**Figure 16**). The raw data are filtered and mathematical algorithms applied to generate values. RV longitudinal strain was

measured from the RV focused apical four-chamber view, in accordance with Task Force standardisation consensus recommendations (Badano *et al.*, 2018). Similar to LV strain, the region of interest included both the RV free wall and interventricular septum at a frame rate of 60 to 90 frames per second. However, since the interventricular septum is traditionally considered a constituent part of the LV, (and is utilised in the assessment of LV strain), RV free wall strain parameters were taken as the arithmetic mean of the base, mid-wall, and apical free wall segment in accordance with expert consensus (**Figure 16)** (Badano *et al.*, 2018). All images were analysed offline using 2D speckle-tracking analysis (EchoPac, V202, GE Healthcare). Frame by-frame data were exported to bespoke software (2D Strain Analysis Tool; Stuttgart, Germany), and cubic spline interpolation was applied. Raw data were normalised to the percentage of systolic and diastolic duration using cubic spline interpolation of systolic (600 data points from the peak of the R wave on the ECG to aortic or pulmonary valve closure for the LV and RV, respectively) and diastolic data (600 data points from aortic or pulmonary valve closure to peak R wave on ECG), resulting in 1200 data points across the cardiac cycle. Thus, the time it took to achieve peak strain and strain rate from the onset of systole were expressed as a percentage of the cardiac cycle, in accordance with previous work (Stöhr *et al.*, 2011; Oxborough *et al.*, 2012*b*; Stembridge *et al.*, 2014).
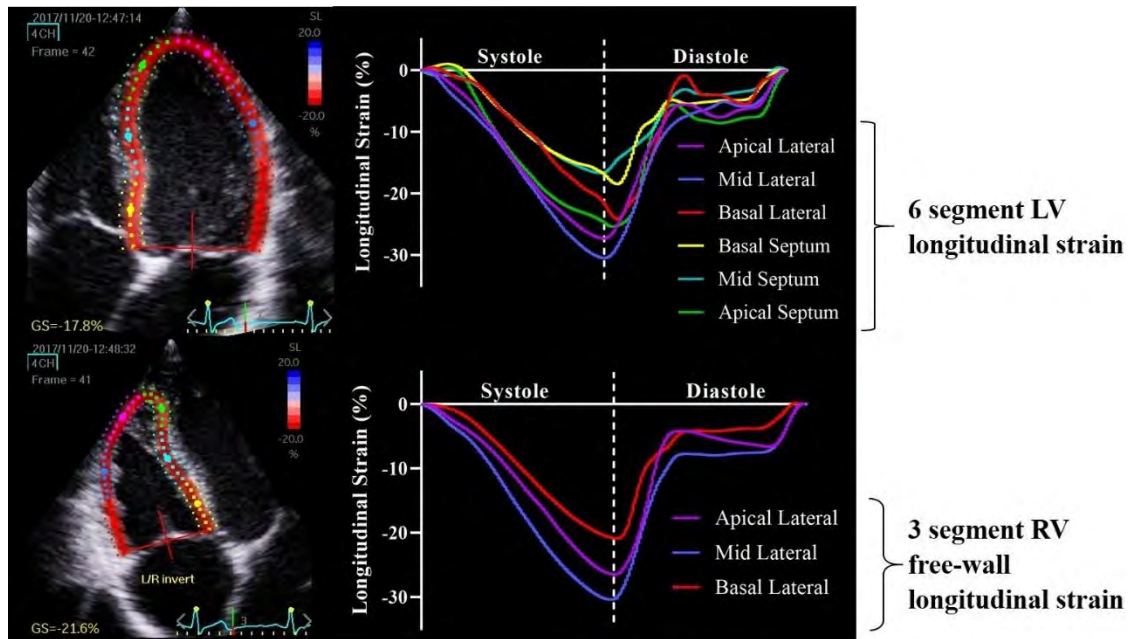
Figure 16. Speckle tracking derived assessment of left ventricular (LV) and right ventricular (RV) strain.

LV longitudinal strain from a conventional apical four chamber view (left) and RV longitudinal strain from an RV focused apical four chamber view (right), taking care to open up the base of the RV and include the apex within the sector width throughout the cardiac cycle. LV longitudinal strain is presented as a 6-segment average, including septal regions, whilst RV free-wall longitudinal strain is reported as a 3-segment, excluding septal strain values.

3.6.5 Echocardiographic Assessment Procedures

All transthoracic echocardiography examinations were performed using a commercially available ultrasound machine (Vivid E9, GE Healthcare, Chalfont St. Giles, Bucks, UK) with a 1.5 to 4.6 MHz-phased array transducer. The specific ultrasound procedures employed in each study is referred to in the methods section of the respective study chapters.

The primary (principal) investigator (Tony Dawkins) engaged in an extensive echocardiography training programme led by an experienced clinical sonographer, and was responsible for a large proportion of echocardiography assessments. Measurement

reliability data for the principal investigator (Tony Dawkins) is presented in Chapter 3.6. Due to the overlap between echocardiography training and data collection, it was necessary to enrol other trained sonographers during the early phase of data collection. However, for consistency the same sonographer was responsible for subsequent assessments of the same participant.

All echocardiographic assessments took place with the participant in the left lateral decubitus position. Echocardiographic images were acquired from three acoustic windows: the parasternal, apical and subcostal windows. All images were acquired in accordance with guidelines from the American society of Echocardiography for the LV (Lang *et al.*, 2006) and RV (Rudski *et al.*, 2010). Images were analysed off-line (EchoPac, GE Healthcare), with measurements taken as an average of three cardiac cycles. An integrated 3-lead ECG on the ultrasound device was obtained to guide echocardiographic analysis.

3.7 Reliability of Echocardiographic Measures

Error may be introduced in echocardiographic measurement due to edge identification and transducer position during imaging (Bellenger *et al.*, 2000). Accuracy of assessment is highly operator dependent. Clear image acquisition and correct interpretation of the images is determined by the skill and variability of the sonographer. Inter and intra-observer reliability in echocardiography has been previously reported, with small coefficient of variation values reported (representing a reliably consistent measurement). For example, the coefficient of variation (CoV) for linear dimensions are reportedly as low as 3.2%, 4.4%, 7.7%, 10.3% for LVIDd, LVIDs, LVPWd, and IVsd, respectively (Ladipo *et al.*, 1980) and 3%, 4.6%, 5% for tissue Doppler derived E' A' and E':A', respectively (Nagueh *et al.*, 1997). Additionally, inter and intra-observer reproducibility of LV GLS has been reported to be very good (Oxborough *et al.*, 2012*a*). Nonetheless, it is important to establish

values for individual intra-observer reliability in order to have confidence in the sonographer, in addition to the measurement method.

3.7.1 Reliability Study: Method

Intraobserver reliability of the primary (principal) investigator (Tony Dawkins) was assessed via repeated measurements of LV and RV structure, function in 9 participants following 10 minutes of rest. Echocardiography images were acquired according to the protocols described above, and collected within a 20 minute period. Offline analysis was conducted by the same researcher (TD). Mean values of 3 cardiac cycles were calculated and used for test-retest analysis (Statistical Package for the Social Sciences Version 22, SPSS Inc., Illinois, United States of America).

The mean of the test-retest differences (systematic bias, $\overline{X}_{diff}$) and the standard deviation of the test-retest differences (s_{diff}) were calculated to quantify random variation (1.96 x s_{diff}), allowing quantification of 95% limits of agreement (LoA). The standard error of measurement (SEM) or absolute reliability, was calculated as: $SEM = \pm\, s_{diff} \div \sqrt{2}$ and presented to a 95% probability (SEM x 1.96, 95% SEM). Mean values for pooled data (scan 1 and scan 2) are also provided. Coefficient of variability values were calculated for each participant by dividing the standard deviation for each pair of measurements by their mean values (CV = (SD/mean)*100). Differences between test-retest values for each measurement are listed in **Table 1** and means for both scores were calculated. Bland Altman (Bland & Altman, 1986) plots were created for each parameter Kolmogorov-Smirnov tests of normality were employed to assess the null hypothesis that data were normally distributed.

3.7.2 Reliability Study: Results

3.7.2.1 Left ventricular structure and function

LV structural parameters demonstrated a low CoV (3.5% - 8.2%). Volumetric assessment of the LV from both an apical four chamber and 2 chamber view generated generally good CoV values (5.6% - 8.8%). CoV values for diastolic mitral valve inflow was low during early diastole (5.0%) but high during late diastole (11.3%). Myocardial velocity at the septal annulus demonstrated a moderate degree of variation (5.5% – 7.0%). All CoV values for LV longitudinal strain (3.8%), time-to-peak strain (2.3%) and strain rate (5.4%) were low with narrow LoA.

3.7.2.2 Right ventricular function

CoV values for RV area were moderate during diastole (8.2%) and systole (9.7%). The CoV for RV4CLS and RVFWLS was low (3.8%) with narrow limits of agreement. Variability was also extremely low for time-to-peak global RV longitudinal strain (0.5%), but high for RV longitudinal strain rate (10.0%). Regional longitudinal strain demonstrated moderate-to-low variability from the base to the apex, respectively.

Table 1. Test-retest reliability coefficients for selected echocardiographic parameters (n = 9).

Variable	Mean (Scan 1)	Mean (Scan 2)	Systematic bias $\overline{X}_{diff}$	Random variation 95% LoA (1.96 x s_{diff})	Absolute reliability 95% SEM (1.96 x SEM)	CoV (%)
Heart Rate (beats·min^{-1})	54	52	2	5	3	3.1
Tricuspid Regurgitation (mmHg)	16	15	1.4	5.6	4.0	9.2
LV Structure						
Septal thickness diastole (cm)	0.93	0.98	-0.04	0.27	0.19	8.2
LV posterior wall thickness diastole (cm)	0.91	0.86	0.05	0.17	0.12	6.3
LVIDd (cm)	4.70	4.83	0.14	0.55	0.39	3.5
Aortic Diameter (cm)	1.9	1.9	0.03	0.39	0.28	6.5
A4C LVLd (cm)	8.6	8.9	-0.3	1.1	0.8	3.1
A4C LVLs (cm)	7.1	7.3	0.2	1.4	1.0	5.1
A2C LVLd (cm)	9.3	8.9	0.5	1.0	0.7	3.9
A2C LVLs (cm)	7.6	7.2	0.4	1.0	0.7	5.1
A4C LV EDV (ml)	120	120	0.2	1	16.43	6.5
A4C LV ESV (ml)	55	58	-2.3	12	8.7	7.0
A4C LV EF (%)	55	51	4.4	8	6	6.5
A2C LV EDV (ml)	132	130	1.2	25	17	5.6
A2C LV ESV (ml)	53	52	1.3	13	19	8.8
A2C LV EF (%)	60	61	-1.15	11	7	5.2
LV function						
Mitral E velocity (m·s^{-1})	0.87	0.88	0.01	0.16	0.11	5.0
Mitral A velocity (m·s^{-1})	0.39	0.41	0.01	0.15	0.11	11.3
Mitral E/A ratio	2.38	2.24	0.14	0.69	0.49	10.5
Septal S' (m·s^{-1})	0.09	0.08	0.01	0.02	0.01	7.0
Septal E' (m·s^{-1})	0.15	0.13	0.01	0.02	0.01	7.0
Septal A' (m·s^{-1})	0.08	0.08	0.00	0.02	0.01	5.5
RV Structure						
RV area diastole(cm^2)	21.7	23.3	-1.6	6.8	4.8	8.2
RV area systole(cm^2)	11.8	13.1	-1.4	2.9	2.0	9.7
RV FAC (%)	46	43	3	10.3	7.3	6.9

LV Strain

LV longitudinal strain (%)	-17.2	-17.2	0.01	2.9	2.0	-3.8
LV TTP longitudinal strain (%)	98	101	-2.5	9.4	6.28	2.3
LV longitudinal strain rate ($\%/s^{-1}$)	-0.92	-0.88	-0.03	0.22	0.16	-5.4
RV Strain						
RV global longitudinal strain (%)	-21.2	-20.4	-0.8	3.6	2.5	-5.8
RV global longitudinal strain TTP strain (%)	101	100	0.1	1.6	1.2	0.5
RV global longitudinal strain rate ($\%/s^{-1}$)	1.07	-0.98	-0.09	0.31	0.2	-10.0
RV free wall strain (%)	-26.0	-25.4	-0.53	2.6	1.8	-3.8
RV basal longitudinal strain (%)	-22.2	-22.3	0.12	5.1	3.6	-7.3
RV mid longitudinal strain (%)	-27.5	-26.8	-0.65	4.57	3.2	-5.7
RV apical longitudinal strain (%)	-28.2	-27.1	-1.1	3.0	2.1	-3.7

LVIDd, left ventricular internal diameter during diastole; LVIDs, left ventricular internal diameter during systole; A4C, apical 4 chamber; A2C, apical 2 chamber; LVLd, left ventricle length in diastole; LVLs, left ventricle length in systole; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; RV, right ventricle; FAC, fractional area change; E, peak early diastolic flow velocity; A, peak late diastolic flow velocity; S', peak systolic annular myocardial tissue velocity; E', peak early diastolic annular myocardial tissue velocity; A', peak late diastolic annular myocardial tissue velocity; TTP, time-to-peak.

3.7.3 Reliability Study: Discussion & Conclusion

The reliability of intra-investigator echocardiography measurements were examined in preparation for prospective data collection within the current thesis. All parameters were within the acceptable CoV limit (< 20%). Intra-observer reliability for LV longitudinal strain measurements were similar to those of others using the same analysis software (Oxborough *et al.*, 2012*a*; Stembridge *et al.*, 2014). Measurements for RV strain were also in close agreement with expert guidance (mean RV global longitudinal strain values 22.3 ± 2.4%, and mean RV free wall longitudinal strain values 28.5 ± 4.8%; (Badano *et al.*, 2020). Overall, this study demonstrated good reproducibility of echocardiography measures obtained and analysed by TD. LV and RV speckle tracking derived longitudinal strain parameters were low, and re-test variation was similar to values previously observed by others (Oxborough *et al.*, 2012*a*).

3.8 Statistical Analyses

Prior to data collection, a power analysis was performed to ensure the studies would be sufficiently powered to detect a given effect size. In a previous study, isometric hand-grip resulted in a 21 ± 11% reduction in SV in long-distance runners vs 4 ± 4% reduction in football linemen (i.e., resistance-trained group) (Shave *et al.*, 2019). Utilising these values, a pooled standard deviation (SD$_{pooled}$) of 8.2% was calculated:

$$SD_{Pooled} = \sqrt{\frac{SD_{group\,1}{}^2 + SD_{group\,2}{}^2}{2}} = \sqrt{\frac{11^2 + 4^2}{2}} = 8.2$$

And an effect size $d = 2$ was computed:

$$\text{Cohen's } d = \frac{Mean_{group\,1} - Mean_{group\,2}}{SD_{Pooled}} = \frac{21 - 4}{2.0} = 2$$

Cohen's d effect size was then transformed to provide a partial eta squared (n^2) of 0.5 and an effect size f of 1.0 (Cohen, 1988). Using this data to inform a power calculation, a total sample size of 33 participants would be required (11 participants in each group) for the study to be sufficiently powered (0.95), with a one-tailed alpha of 0.05. As such, 15 participants were aimed to be recruited in each group due to the potential difficulty with image acquisition during experimental procedures employed in this thesis and potential participant attrition.

Statistical analyses for experimental **Chapter 5 and 6** were conducted using the Statistical Package for the Social Sciences version 24 (SPSS Inc, IL, USA). All data were first assessed for normality using the Shapiro-Wilk test and visual inspection of Q-Q plots. Alpha level was set at < 0.05 and data were expressed as means ± standard deviation (SD). A detailed description of the statistical analyses conducted for each study can be found in the methodology section of each experimental chapter. For all main outcomes, Cohens d was reported as an estimate of effect size (0.2 = small effect, 0.5 = medium effect, 0.8 = large effect).

Chapter 4

Right Ventricular function and region-specific adaptation in athletes: A meta-analysis

Chapter 4. Right ventricular function and region-specific adaptation in athletes engaged in high-dynamic sports: A meta-analysis

A version of this thesis chapter has been accepted for publication in Circulation: Cardiovascular Imaging (Appendix VIII)

4.1 Introduction

While left ventricular remodelling in response to exercise training has been extensively studied (Fagard, 1996; Whyte *et al.*, 2004; Utomi *et al.*, 2013; Beaumont *et al.*, 2017*a*; Lord *et al.*, 2018; Wundersitz *et al.*, 2020) the RV has received comparatively less attention until recent years. This is, in part, due to the anatomical complexity of the crescentic RV shape which has made routine imaging technically challenging (Ho & Nihoyannopoulos, 2006). Advances in cardiac imaging have recently enabled a more detailed RV assessment and have identified significant potential for exercise-induced remodelling (La Gerche *et al.*, 2017). Remodelling of the heart in response to endurance training has long been considered the result of an increased haemodynamic 'volume' load (Morganroth *et al.*, 1975); however, it is now accepted that dynamic exercise (i.e., exercise involving rhythmic muscular contractions causing a marked increase in oxygen consumption, heart rate and cardiac output (Levine *et al.*, 2015) may also be associated with an increased 'pressure' as well as 'volume' stimulus, particularly of the RV (Haykowsky *et al.*, 2018). In the RV, wall stress is low at rest, corresponding with low pressures in the pulmonary circuit, which the RV must overcome to achieve ejection. During high-dynamic exercise, however, RVSP

increases in order to drive SV in the face of higher downstream PASP, secondary to high circulatory flow (La Gerche *et al.*, 2010). In addition to the high RV load experienced during high-dynamic exercise, athletes may also be exposed to an elevated hemodynamic load, owing to an expanded blood volume (Convertino, 1991) and an increased RVSP at rest (D'Andrea *et al.*, 2011; Mirea *et al.*, 2018); although the latter has not been consistently reported (La Gerche *et al.*, 2010; Pagourelias *et al.*, 2013; Boczar *et al.*, 2019; Claeys *et al.*, 2020).

Structural remodelling of the RV in response to exercise-training, including increased end-diastolic volume or area, basal dilatation and a highly trabeculated apex, has been widely evidenced in endurance athletes from high-dynamic sports (Oxborough *et al.*, 2012*b*; D'Andrea *et al.*, 2013; D'Ascenzi *et al.*, 2017*b*) and is used to differentiate pathology in sports cardiology (Prior, 2018). However, functional adaptation of the RV is less clear. In contrast to the LV, in which the myofibers are arranged helically (Sengupta *et al.*, 2006), RV contraction is predominantly driven by longitudinal shortening of the RV free-wall and interventricular septum, with contribution from circumferential muscle fibre constriction and late infundibular contraction (Ho & Nihoyannopoulos, 2006; Buckberg & Hoffman, 2014). Systolic function assessed as ejection fraction or fractional area change is preserved or slightly reduced with increasing SV in athletes (La Gerche *et al.*, 2011; D'Ascenzi *et al.*, 2017*b*, 2017*a*). Yet, conflicting results of either greater (D'Andrea *et al.*, 2007; La Gerche *et al.*, 2010), lower (D'Andrea *et al.*, 2020), or unchanged (Utomi *et al.*, 2015; D'Ascenzi *et al.*, 2017*a*) indices of global systolic function have been reported in athletes. Furthermore, consistent with structural remodelling (Teske *et al.*, 2009; La Gerche *et al.*, 2012*a*), functional adaptation may be region-specific, affecting the base and the apex of the RV differentially. For example, resting RV basal longitudinal deformation may be lower, and apical deformation greater, among highly trained endurance athletes (Teske *et al.*, 2009; La Gerche *et al.*, 2012*a*; Mirea *et al.*, 2018), which may be due to altered

hemodynamic loading conditions, intrinsic myocardial adaptation and/or structural remodelling. Although these studies have provided a unique insight, a comprehensive meta-analysis of exercise-induced functional remodelling of the RV has not been undertaken. Consequently, the aims of this meta-analysis were to investigate the influence of long-term exercise training on (i) RVSP at rest and during exercise and (ii) RV free-wall and regional systolic functional adaptation. To address these aims, the following parameters were compared between athletes from high-dynamic sports and controls: RVSP, tricuspid annulus displacement and velocity and RV free-wall deformation. It was hypothesised that an analysis of studies that have assessed RV systolic function in athletes would provide evidence of an elevated RV systolic pressures at rest, and region-specific functional remodelling.

4.2 Methods

4.2.1 Protocol

This meta-analysis was registered *a priori* with PROSPERO, the international prospective register of systematic reviews (Registration no. CRD42020206091; **Appendix VI**) and conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher *et al.*, 2015).

4.2.2 Search Strategy and Inclusion Criteria

The participants, interventions, comparisons, outcomes, and study design (PICOS) framework was used to guide this study.

4.2.2.1 Participants

The population of interest were humanathletes (aged ≥ 18 years) from sports with a high-dynamic component, as defined by the Mitchell criteria (i.e., regular contraction of large muscle groups and sustained increase in oxygen consumption) (Levine *et al.*, 2015).

4.2.2.2 Intervention

No intervention was required.

4.2.2.3 Comparison

The comparator was a non-athletic (exercising < 3 hours per week) control group (aged $\geq$ 18 years), without history or evidence of current or chronic cardiovascular, respiratory or metabolic disease.

4.2.2.4 Outcome variables

Primary outcome variables included RVSP obtained by non-invasive echocardiography or invasively by right-heart catheterization, i) at rest, and ii) in response to dynamic exercise matched to an absolute or relative exercise intensity between groups. Other measures of RV systolic function obtained at rest included TAPSE, systolic myocardial velocities (S'), and measures of free-wall and regional (base and apex) longitudinal strain and strain rate; obtained via echocardiography or cMRI. RV free-wall strain was taken as the arithmetic mean of the three segments of the RV free-wall. RV chamber dimensions and areas were also extracted.

4.2.2.5 Study designs

Original publications written in English were included. Reviews, editorials, case reports and unpublished data were excluded. Studies of longitudinal design were eligible to be included, providing the training intervention was > 2 years in duration and the weekly training volume > 6 hours/week.

4.2.2.6 Information sources

A comprehensive search of peer-reviewed studies published prior to June 4th, 2020 that examined RVSP and RV systolic function was conducted. Specifically, publicly available databases (PubMed, MEDLINE, Scopus, Science Direct and Web of Science) were

searched using the following search string: *"Right ventric* OR pulmonary arter* OR pulmonary pressure AND function* OR strain OR mechanics OR adaptation OR remodel* OR response OR exercise OR deformation* AND athlete OR endurance."* Reference lists from included articles were also examined in order to identify any additional relevant studies. Authors were contacted for data and/or methodological clarification where necessary.

4.2.3 Study Review and Data Extraction

Titles and abstracts of identified publications were screened using an online reviewing software (Covidence, Veritas Health Innovation Ltd, Australia). Full text articles were retrieved for studies that were considered relevant from the initial evaluation. Full text articles were then independently assessed for eligibility against PICOS inclusion criteria by two reviewers (Tony Dawkins and Bryony Curry); conflicts were resolved through discussion or by a third reviewer (Dr Mike Stembridge). Studies were excluded if they: did not report relevant outcome measures (n = 99), did not include a control population (n = 68), was not an original article (n = 19), was not written in English (n = 8), mean age was <18 years old (n = 7), repeated data from another included study (n = 4), athletic training duration was less than 2 years (n = 5), participants were not from a stated sporting discipline with a high-dynamic component, according to the Mitchell categorisation (n = 6).

Age, sex, training status and training mode of participants were recorded, and measures of RVSP and RV function were extracted. Where strain and strain rate data were acquired using both speckle tracking echocardiography (STE) and Doppler echocardiography, only STE derived strain data was extracted. Where athletes were reported by sex, studies were subcategorized as males (M) and females (F), providing relevant control populations were included. Where there were multiple athletic subgroups but only one control population, data were extracted only from the athletic group performing the greatest volume (hours) of dynamic exercise. If relevant data were included

in graphical format, numerical data were retrieved using a reliable open-source software program (WebPlotDigitizer, version 4.3). Data presented as median and range were transformed to mean and standard deviation (SD) (Wan *et al.*, 2014). Data presented as mean and confidence interval (CI) were transformed to mean and SD using the following formula: SD= $\sqrt{n}$x (Upper limit of CI – Lower limit of CI)/3.92. A critical appraisal of methodological quality for each study was performed according to the National Institute of Health (NIH) 'guidance for assessing the quality of observational cohort and cross-sectional studies' (https://www.nhlbi.nih.gov/health- topics/study-quality-assessment-tools).

4.2.4 Statistical Analyses

Meta-analyses were computed using the DerSimonian and Laird method (DerSimonian & Laird, 1986) and applied to all continuous primary variables to determine the weighted mean difference (WMD) and 95% CI between control participants and athletes. WMD corresponding to a small Cohen's d effect size (0.2) were considered the minimum clinically important difference (MCID) (Copay *et al.*, 2007). The pooled estimate for the lower and upper reference value (mean value $\pm$ 2 SD's) were calculated, with 95% CI for further robustness. A random-effects model was based upon an *a priori* decision, reflecting the anticipated heterogeneity of the data, owing to the potential variety of sporting disciplines, athletic training status (i.e., training type, volume, intensity and load), and methodological differences in data acquisition. Between-study heterogeneity was evaluated using Chi-squared (χ^2) with a *P* value < 0.05 indicating significant heterogeneity, and the percentage of variability in the effect estimates that was due to heterogeneity evaluated using the inconsistency index (I^2) (Higgins *et al.*, 2003). Publication bias was assessed using funnel plots and the Egger regression method, with a *P* value < 0.1 considered significant for asymmetry (Egger *et al.*, 1997). Correction factors such as the trim and fill method were not applied due to the known poor performance in the presence of between-

study heterogeneity. Since each study utilised the same scoring system for each parameter, data were analysed as weighted mean differences (WMD). As such, it was not deemed necessary to transform data into standard mean differences. Forest plots were created using Review Manager (RevMan [Computer program] Version 5.4, The Cochrane Collaboration, 2020) and presented as compiled figures. To explore potential relationships, random effects meta-regressions for age, sex and training hours were conducted for each parameter using the 'metareg' command in Stata (Version 16). Subgroup analysis was also performed to investigate heterogeneous results and the potential influence of covariates by dividing studies using categorical variables (age, sex, training hours and, operating vendor for strain parameter). RVSP/cardiac output slopes (i.e., increase in RVSP per unit increase in cardiac output) were calculated for each study by dividing the increase in mean RVSP from baseline to exercise by the increase in mean cardiac output. Grouped mean slopes were compared using an independent samples t-test (Graphpad Prism, version 8.4.2; GraphPad Software Inc., San Diego, CA, USA).

4.3 Results

4.3.1 Study Selection

Figure 17 provides a summary of the study selection, included studies and number of participants for each outcome variable. From the 1,974 studies identified in the initial search, 53 studies involving 2908 athletes and 2614 controls were included in the final analyses of all variables. Two studies reporting RVSP were excluded due to duplication of study data, which was clarified via correspondence with the authors (La Gerche *et al.*, 2011; D'Andrea *et al.*, 2012). Three studies reported athletic and control datasets for both males and females (Mansencal *et al.*, 2007; Sanz-de la Garza *et al.*, 2017a; Lakatos *et al.*, 2018). RVSP was assessed via echocardiographic assessment of tricuspid regurgitant velocity in 20 of 21 included studies. One study collected RVSP invasively via balloon tipped catheter (Wright *et al.*, 2019). Further details of individual studies including the PubMed unique

identifier (PMID) are included in **Appendix II: Supplementary Table 1**. In total, 11 studies were rated good, 39 studies were rated fair, and 3 studies were rated poor. Of the 3 studies that were considered poor, 2 reported TAPSE and 1 reported RV S'. For studies reporting RVSP at rest, 6 were considered good, 14 were considered fair, and 0 were considered poor. For RVSP during exercise, 3 were considered good, 5 were considered fair, and 0 were considered poor. Finally, for RV longitudinal strain, 4 were considered good, 18 were considered fair and 0 were considered poor (Supplementary Table 4).
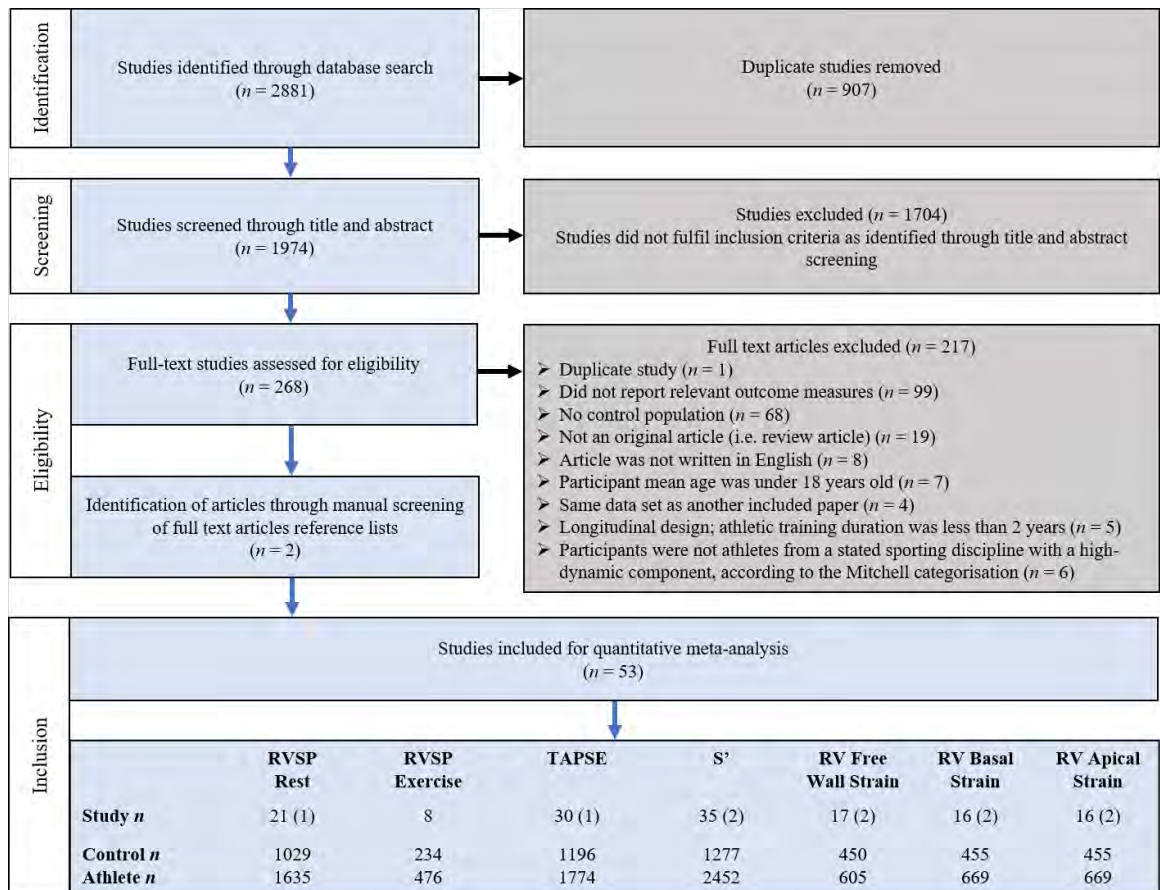
Figure 17. Flow diagram showing study inclusion and exclusion processes.

RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; S', systolic myocardial velocity. Brackets after study n indicate where studies have been split into sub-studies, where sex has been explicitly differentiated.

The total number of studies included for each primary outcome variable differs and is highlighted in **Figure 17**. In agreement with previous analyses, RV dimensions were consistently greater in athletes compared with controls (**Table 3**). Meta-analysis of RVSP at rest, and in response to exercise, revealed a WMD between the athletes and controls of 2.9 mmHg (95% CI, 1.3 to 4.5 mmHg) and 11.0 mmHg (95% CI 6.5 to 15.6 mmHg), respectively (**Figure 18, Table 2**). Normative reference ranges obtained for each parameter are provided in **Table 3**. Statistical heterogeneity was observed both at rest (Chi^2 306, P < 0.0001; I^2 value of 93%) and during exercise (Chi^2 34, P < 0.0001; I^2 value of 79%). There was evidence of publication bias for RVSP both at rest (Egger's test 2.85, P = 0.013) and during exercise (Egger's test 2.69, P = 0.036). From rest to exercise, there was no significant difference in the slope of mean RVSP increase per unit increase in mean cardiac output between groups (

Table 3. Meta-analysis results comparing the weighted mean difference for right ventricular dimensions and areas between athletes and non-athletic controls.

Parameter	Study *n* (Participant *n* Control:Athlete)	MCID 0.2*SDpooled	WMD (95% CI)	Effect size Cohen's d	Z	P value	I2
RV basal diameter (mm)	19 (924:1986)	1.0	-4.7 (-5.9, -3.5)	1.0	7.77	<0.0001	86
RV mid-cavity diameter (mm)	9 (680:1137)	0.9	-5.3 (-6.9, -3.6)	1.1	6.13	<0.0001	91
RV length (mm)	12 (512:818)	1.5	-6.4 (-8.7, -4.1)	0.8	5.42	<0.0001	82
RVOT Proximal PLAX (mm)	7 (380:639)	1.0	-4 (-5, -3)	0.9	6.22	<0.0001	87
RVOT Proximal PSAX (mm)	4 (100:232)	0.9	-3 (-5, -1)	0.7	3.04	0.002	71
RVOT Distal PSAX (mm)	4 (501:884)	1.2	-3 (-3, -2)	0.4	7.26	<0.0001	89
RV EDA (ml)	15 (367:1058)	0.8	-6.5 (-9.9, -3.2)	1.9	3.8	0.0001	98
RV EDA index (ml·m2)	8 (252:303)	0.3	-1.57 (-1.85, -1.28)	0.9	10.8	<0.0001	84
RV ESA (ml)	14 (549:1362)	0.5	-3.5 (-5.4, 1.7)	1.6	3.78	0.0002	97
RV ESA index (ml·m2)	5 (84:105)	0.2	-14.4 (-16.4, -12.5)	0.8	14.47	<0.0001	29

| FAC (%) | 24 (848:1857) | 1.2 | 0.60 (-0.41, 1.61) | -0.1 | 1.60 | 0.25 | 73 |

RV, right ventricle; RVOT, right ventricular outflow tract; PLAX, parasternal long axis; PSAX, parasternal short axis; EDA, end-diastolic area; ESA, end-systolic area.

Figure *19*).

Table 2. Characteristics of studies used in meta-analysis of right ventricular systolic pressure in athletes and non-athletic controls

Study	Athlete Type	*n* athlete	*n* control	Male (%)	Age, years Control	Age, years Athlete	Training hours	Training years	RVSP Methodology	Body Position	Exercise Method
Bossone 1999	Varsity ice hockey players	26	14	CT: 100; A: 100	18.9 ± 0.9	20.3 ± 1.7	NS	NS	Echo	Left lateral	Cycling at 240 watts
Claessen 2016	Endurance athletes	19	9	NS	NS	NS	NS	NS	Echo	Semi-supine for echo and supine for MRI	During peak semi-supine cycling exercise (66% of peak upright power output)
Claeys 2020	Regular endurance athlete	20	20	CT: 100; A: 100	37 ± 13	34 ± 8	14 (8-16)	10 (6-21)	Echo	Lateral tilt semi supine	During semi-supine cycling exercise (60% of peak upright power output)
D'Andrea 2011	Long- and middle-distance swimming or running, soccer, and basketball	370	230	CT: 61; A: 62	27.5 ± 11.3	28.8 ± 10.1	15-20	>4 years	Echo	Left lateral	NA
D'Andrea 2012	Long- and middle-distance swimming or running, soccer, or basketball	220	250	CT: 58; A: 66	27.8 ± 10.3	28.4 ± 11.1	15-20	>4 years	Echo	Not stated	NA
D'Andrea 2013	Long- and middle-distance swimming or running, soccer, and basketball	395	230	CT: 61; A: 61	25.2 ± 3.92	28.8 ± 10.1	15-20	>4 years	Echo	Not stated	NA

D'Andrea 2020	Long- and middle-distance swimmers, runners and cyclists	370	230	CT: 57; A: 59	32.4 ± 5.1	31.6 ± 4.2	15-20	>5 years	Echo	Not stated	During peak semi-supine cycling exercise (25 w/ 2 min incremental)
Esposito 2014	Competitive rowers	40	43	CT: 100; A: 100	29 ± 5.8	28.4 ± 9.5	>30	4-12 years	Echo	Not stated	NA
King 2013	Elite rowers	18	17	CT: 100; A: 100	27.1 ± 3.5	22.4 ± 3.7	5 to 11	NS	Echo	Not stated	NA
Kuchynka 2010	Competitive amateur cyclists	51	47	CT: 100; A: 100	24 ± 2	24 ± 3	>2 hrs 3 days/week)	NS	Echo	Not stated	NA
LaGerche 2010	Endurance sports	40	15	CT: 87; A: 90	38 ± 6	36 ± 8	16 ± 5	NS	Echo	Not stated	During peak semi-supine cycling exercise (25 w/ 2 min incremental)
LaGerche 2011	Endurance cycling, running and triathlon	39	14	CT: 86; A: 90	38 ± 6	36 ± 8	16 ± 5	10 ± 9	Echo	Semi-supine	During peak semi-supine cycling exercise (12.5w/min incremental)
LaGerche 2015	Cyclists and runners	10	7	CT: 86; A: 84	34 ± 16	35 ± 6	10.6 ± 7.7	10.8 ± 9.5	Echo	Left lateral tilt	During peak semi-supine cycling exercise (66% of peak upright power output)
Mansencal 2007 (F)	Professional tennis players	30	30	CT: 0; A: 0	22.2 ± 4.5	22.2 ± 4.5	NS	NS	Echo	Not stated	NA
Mansencal 2007 (M)	Professional tennis players	50	50	CT: 100; A: 100	24.9 ± 4.1	24.9 ± 4.1	NS	NS	Echo	Not stated	NA

Study	Population								Modality	Position	Protocol
Pagourelias 2013	Endurance cycling, running and triathlon	80	26	CT: 100; A: 100	26.6 ± 5.6	31.2 ± 10.4	14.6 ± 5.4	11.3 ± 8.3	Echo	Not stated	NA
Rimensberger 2014	Ultra-endurance runners	26	33	CT: 100; A: 100	41 ± 7	44 ± 9	7 ± 8.5	15 ± 19.6	Echo	Not stated	NA
Sanchis-Gomar 2016	Elite runners and cyclists	11	18	CT: 100; A: 100	58 ± 5	54 ± 4	10.6 ± 3.1	29 ± 9	Echo	Not stated	NA
Tran 2019	Ironman athletes	20	20	CT: 50; A: 85	42.6 ± 7	39.5 ± 11.3	NS	NS	Echo	Not stated	Post treadmill Bruce or accelerated Bruce protocol for control and athlete, respectively
Utomi 2015	Elite Ultra Endurance Runners	19	21	CT: 100; A: 100	27 ± 8	34 ± 5	12 h/week	11 years	Echo	left lateral decubitus	NA
Vitarelli 2013	Marathon Runners	35	35	CT: 100; A: 100	28.3 ± 11.4	28.7 ± 10.7	NS	9.6 ± 2.9	Echo	left lateral recumbent position	NA
Wright 2019	Endurance trained	5	10	CT: 30; A: 100	55.8 ± 6.2	54.6 ± 3.4	>6 hours per week	>10 years	RV balloon catheter	semi-upright 30-degree incline)	Moderate cycling exercise, at a target heart rate of 120 bpm (untrained) or 130 bpm (trained) for 8-10 min.

Three studies were included following email contact, as outcome variables were collected but not reported. (Claessen et al., 2016; Utomi et al., 2015; Wright et al., 2019) CT, control; A, athlete; NS, not stated; NA, not applicable.
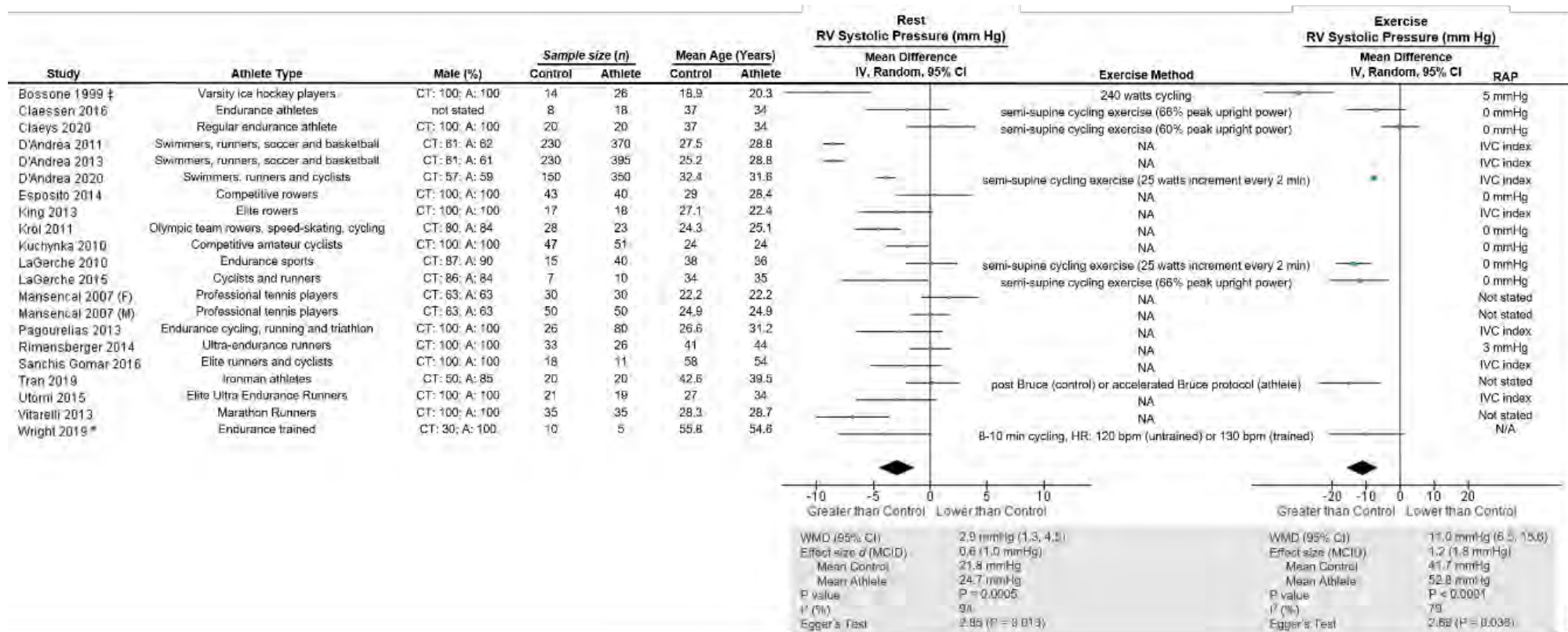
Figure 18. Individual forest plots of right ventricular pressure at rest and during exercise.

Weighted mean difference (WMD), 95% confidence intervals, effect size (Cohen's *d*) and minimum clinically important difference (MCID) for studies included in meta-analysis of right ventricular systolic pressure (RVSP) at rest (21 studies, Control *n* = 1029; Athlete *n* = 1635) and during exercise (8 studies, Control *n* = 234; Athlete *n* = 476). The mean age across studies was 31 years for both athletes and control populations. NA; not applicable since exercise was not performed in this study. ‡ numerical data were retrieved from graphical format. * pressure measurements were obtained via invasive balloon catheter. All other studies used transthoracic echocardiography to estimate RVSP from the tricuspid regurgitant velocity. RAP, right atrial pressure.

Table 3. Meta-analysis results comparing the weighted mean difference for right ventricular dimensions and areas between athletes and non-athletic controls.

Parameter	Study n (Participant n Control:Athlete)	MCID 0.2*SD$_{pooled}$	WMD (95% CI)	Effect size Cohen's d	Z	P value	I^2
RV basal diameter (mm)	19 (924:1986)	1.0	-4.7 (-5.9, -3.5)	1.0	7.77	<0.0001	86
RV mid-cavity diameter (mm)	9 (680:1137)	0.9	-5.3 (-6.9, -3.6)	1.1	6.13	<0.0001	91
RV length (mm)	12 (512:818)	1.5	-6.4 (-8.7, -4.1)	0.8	5.42	<0.0001	82
RVOT Proximal PLAX (mm)	7 (380:639)	1.0	-4 (-5, -3)	0.9	6.22	<0.0001	87
RVOT Proximal PSAX (mm)	4 (100:232)	0.9	-3 (-5, -1)	0.7	3.04	0.002	71
RVOT Distal PSAX (mm)	4 (501:884)	1.2	-3 (-3, -2)	0.4	7.26	<0.0001	89
RV EDA (ml)	15 (367:1058)	0.8	-6.5 (-9.9, -3.2)	1.9	3.8	0.0001	98
RV EDA index (ml·m^2)	8 (252:303)	0.3	-1.57 (-1.85, -1.28)	0.9	10.8	<0.0001	84
RV ESA (ml)	14 (549:1362)	0.5	-3.5 (-5.4, 1.7)	1.6	3.78	0.0002	97
RV ESA index (ml·m^2)	5 (84:105)	0.2	-14.4 (-16.4, -12.5)	0.8	14.47	<0.0001	29
FAC (%)	24 (848:1857)	1.2	0.60 (-0.41, 1.61)	-0.1	1.60	0.25	73

RV, right ventricle; RVOT, right ventricular outflow tract; PLAX, parasternal long axis; PSAX, parasternal short axis; EDA, end-diastolic area; ESA, end-systolic area.

Figure 19. Mean right ventricular systolic pressure (RVSP) and cardiac output values for each study are presented where possible (error bars represent 95% CI), with slopes intersecting mean baseline and exercise data.

Grouped mean slopes are represented by dashed black lines for non-athletic controls and solid blue lines for athletes. * pressure measurements were obtained via invasive balloon catheter. All other studies used transthoracic echocardiography to estimate RVSP from the tricuspid regurgitant velocity.

4.3.3 Right Ventricular Systolic Function

TAPSE and S' were greater in athletes than in controls (**Table 5** and **Table 6; Appendix II: Supplementary Figure 1 and 2**). RV global (6-segment) and free-wall (3-segment) longitudinal strain were not different between athletes and controls (P = 0.22). However, regional strain at the apex was greater (more negative) in athletes (WMD 0.9%, 95% CI 0.1 to 1.8%; P = 0.04), but lower at the base in athletes compared to controls (WMD -2.5%, 95% CI -1.4 to -3.5%, P < 0.0001; **Figure 20**). Mid-wall strain was not significantly different between athletes and controls (WMD -0.11%, 95% CI -0.73, 0.51%, P = 0.72). For all primary outcome variables, there was significant evidence of high study-to-study heterogeneity, but no statistical evidence of publication bias from visual inspection of funnel plots and using Egger's test (**Figure 20**).

RV free-wall strain rate was lower in athletes compared with controls (WMD -0.13 s^{-1}, 95% CI -0.08 to -0.19 s^{-1}, P = 0.0001, **Table 5 and Table 6; Appendix II: Supplementary Figure 3**). Strain rate in athletes was also lower at the base of the RV (WMD -0.26 s^{-1}, 95% CI -0.06 to -0.46 s^{-1}, P = 0.01), but not at the mid wall (WMD -0.10 s^{-1}, 95% CI -0.24, 0.03 s^{-1}, P = 0.), or apex (WMD -0.02 s^{-1}, 95% CI 0.05 to -0.09, P = 0.60).

Table 4. Characteristics of studies used in meta-analysis of right ventricular strain in athletes and non-athletic controls

Study	Athlete Type	n Athlete	n Control	Male %	Age, years Athlete	Age, years Control	Training hours / wk	Training years	Strain Methodology	RV strain Software system
Bernheim 2013	Ironman	39	23	CT: 78; A: 82	36.7 ± 9.2	36.7 ± 9.5	NS	NS	2D STE, 6 segment ROI	GE
Bohm 2016	Elite master endurance athletes	33	33	CT: 100; A: 100	47 ± 8	46 ± 9	16.7 ± 4.4	29 ± 8	2D STE, 6 segment ROI	GE
Claeys 2020	Regular endurance athletes	17	12	CT: 100; A: 100	34 ± 8	37 ± 13	14 (8-16)	10 (6-21)	2D STE, 3 segment ROI	GE
Doronina 2018	Water polo (national team)	15	15	CT: 0; A: 0	24 ± 4	23 ± 2	24 ± 8	12.1 ± 4.6	3D STE	TomTech
Esposito 2014	Competitive Rowers	40	43	CT: 100; A: 100	28.4 ± 9.5	29 ± 5.8	NS	NS	2D STE, 6 segment ROI	GE
Kooreman 2019	College Rowers, lacrosse, water polo	37	31	CT: 0; A: 0	19 ± 1	19 ± 1	NS	NS	2D STE. ROI not stated	TomTech
LaGerche 2012	Endurance athletes (marathon, endurance cycling, or triathlon)	40	15	CT: 87; A: 90	37 ± 8	38 ± 6	16.3 ± 5.1	NS	2D STE, 6 segment ROI	GE
LaGerche 2015	Cyclists and runners	10	7	CT: 100; A: 100	35 ± 6	34 ± 16	10.6 ± 7.7	10.8 ± 9.5	2D STE, 6 segment ROI	GE
Lakatos 2018 (F)	Water polo (national team)	30	20	CT: 0; A: 0	19 ± 3.7	19.5 ± 2.3	17 ± 6	10 ± 5	3D STE	TomTech
Lakatos 2018 (M)	Water polo (national team)	30	20	CT: 100; A: 100	18.9 ± 4	19.9 ± 3.8	17 ± 6	10 ± 5	3D STE	TomTech
Pagourelias 2013	National and International level endurance cyclists, runners, and triathletes	80	26	CT: 100; A: 100	31.2 ± 10.4	26.6 ± 5.6	14.6 ± 5.4	11.3 ± 8.3	2D STE, 6 segment ROI	GE

Study	Population								Method	Vendor
Popple 2018	Elite Soccer Players	100	20	CT: 100; A: 100	25 ± 5	25 ± 4	20	NS	2D STE, 3 segment ROI	GE
Rimensberger 2014	Ultra-endurance runners	26	33	CT: 100; A: 100	44 ± 9	41 ± 7	7 ± 8.5	15 ± 1.6	2D STE, 6 segment ROI	Philips
Rothwell 2018	Ultra-marathon runners	40	24	CT: 83; A: 83	46 ± 8	46 ± 7	11 ± 4	18 ± 12	2D STE 3 segment ROI	GE
Sanz delaGarza 2017 (F)	Runners	20	20	CT: 0; A: 0	37.4 ± 6.3	36.9 ± 4.6	13.2 ± 1.4	10.2 ± 3.4	2D STE, 6 segment ROI	GE
Sanz delaGarza 2017 (M)	Runners	20	20	CT: 100; A: 100	38 ± 3.5	36.2 ± 3.5	13.5 ± 1.6	10.8 ± 4	2D STE, 6 segment ROI	GE
Simsek 2013	Long-Distance Runners	44	30	CT: 27; A: 27	24.1 ± 2.9	23.8 ± 2.1	14 to 18	NS	2D STE, 6 segment ROI	GE
Sitges 2017	Professional mid-high dynamic sportsmen	100	50	CT: 100; A: 100	25 ± 6	25 ± 4	>18	>5 years	2D STE, 3 segment ROI	GE
Stewart 2020	State/national level cyclists/runners/swimmers/rowers	30	30	CT: 100; A: 100	31 ± 10	29 ± 9	>10	NS	2D STE, 3 segment ROI	GE
Teske 2009	national and international level cyclists, long-distance runners, rowers and triathletes	63	61	CT: 59; A: 70	27 ± 4.7	27.7 ± 5.5	24.2 ± 5.7	NS	2D STE, 3 segment ROI	GE
Utomi 2015	Elite Ultra Endurance Runners	19	21	CT: 100; A: 100	34 ± 5	27 ± 8	12	11	2D STE, 3 segment ROI	GE
Vitarelli 2013	Marathon Runners	35	35	CT: 100; A: 100	28.7 ± 10.7	28.3 ± 11.4	NS	9.6 ± 2.9	2D STE, 6 segment ROI	GE
Zha 2015	Marathon Runners	19	24	CT: 53; A: 53	39 ± 10	45 ± 8	NS	NS	1.5 T cMRI	GE

CT, control; A, athlete; NS, not stated. STE, speckle tracking echocardiography

Study	Athlete Type	Male %	Sample size (n) Control	Sample size (n) Athlete	Mean Age (Years) Control	Mean Age (Years) Athlete	RV Free Wall Strain (%) Mean Difference IV, Random, 95% CI	RV Basal Strain (%) Mean Difference IV, Random, 95% CI	RV Apical Strain (%) Mean Difference IV, Random, 95% CI
Bernheim 2013	Ironman athletes	CT: 78; A: 82	23	39	36.7	36.7			
Bohm 2016	Elite master endurance athletes	CT: 100; A: 100	33	33	46	47			
Claeys 2020	Endurance athletes	CT: 100; A: 100	12	17	37	34			
Doronina 2018	Water polo	CT: 0; A: 0	15	15	23	24			
Esposito 2014	Competitive rowers	CT: 100; A: 100	43	40	29	28.4			
Kooreman 2019	College rowers, lacrosse & water polo	CT: 0; A: 0	31	37	19	19			
LaGerche 2012 ‡	Endurance athletes	CT: 87; A: 90	15	40	38	37			
LaGerche 2015	Cyclists and runners	CT: 100; A: 100	7	10	34	35			
Lakatos 2018 (F)	Water polo (national team)	CT: 50 ; A: 50	20	30	19.5	19			
Lakatos 2018 (M)	Water polo (national team)	CT: 50 ; A: 50	20	30	19.9	18.9			
Pagourelias 2013	Elite endurance cyclists	CT: 100; A: 100	26	80	26.6	31.2			
Popple 2018	Elite soccer players	CT: 100; A: 100	20	100	25	25			
Rimensberger 2014 ‡	Ultra-endurance runners	CT: 100; A: 100	33	26	41	44			
Rothwell 2018	Ultra-marathon runners	CT: 83; A: 83	24	40	46	46			
Sanz delaGarza 2017 (F)	Runners	CT: 50; A: 50	20	20	36.9	37.4			
Sanz delaGarza 2017 (M)	Runners	CT: 50; A: 50	20	20	36.2	38			
Simsek 2013	Long-distance runners	CT: 27; A: 27	30	44	23.8	24.1			
Sitges 2017	Professional mid-high dynamic sports	CT: 100; A: 100	50	100	25	25			
Stewart 2020	Cyclists, runners, swimmers & rowers	CT: 100; A: 100	30	30	29	31			
Swoboda 2016 †	Runners, cyclists and triathletes	CT:77; A: 77	35	35	30.6	31.3			
Teske 2009	Elite cyclists, runners and rowers	CT: 59; A: 70	61	63	27.7	27			
Utomi 2015	Elite ultra-endurance runners	CT: 100; A: 100	21	19	27	34			
Vitarelli 2013	Marathon runners	CT: 100; A: 100	35	35	28.3	28.7			
Zha 2015 †	Marathon runners	CT: 53; A: 53	24	19	45	32.4			

	RV Free Wall Strain (%)	RV Basal Strain (%)	RV Apical Strain (%)
WMD (95% CI)	-0.4% (-1.0, 0.2)	-2.5% (-3.5, -1.4)	0.9% (0.1, 1.8)
Effect size d (MCID)	0.2 (0.6%)	0.8 (0.8%)	0.3 (0.8%)
Mean Control	-26.8%	-25.3%	-28.4%
Mean Athlete	-26.4%	-22.9%	-29.3%
P value	P = 0.22	P < 0.0001	P = 0.04
I² (%)	64	85	71
Egger's Test	-1.35 (P = 0.199)	-1.22 (P = 0.242)	0.97 (P = 0.348)

Figure 20. Individual forest plots for right ventricular free-wall and regional strain.

Weighted mean difference (WMD), 95% confidence intervals, effect size (Cohen's *d*) and minimum clinically important difference (MCID) for studies included in the meta-analysis of right ventricular free-wall (17 studies, Control *n* = 450; Athlete *n* = 605) and region-specific strain (16 studies, Control *n* = 455; Athlete *n* = 669). † strain values were obtained via magnetic resonance imaging. All other studies utilized speckle tracking echocardiography. ‡ numerical data were retrieved from graphical format. Studies differentiating sex were divided into females (F) and males (M). CT, control; A, athlete.

Table 5. Meta-analysis results for displacement and velocity parameters of right ventricular systolic function and strain rate measures in athletes and non-athletic controls.

Parameter	Studies (*n*)	Controls (*n*)	Athletes (*n*)	MCID (0.2 * SD$_{pooled}$)	WMD (95% CI)	Effect size (Cohen's *d*)	P value	I^2	Eggers Test (P value)
TAPSE (mm)	30	1196	1774	0.7	-1.8 (-1.0, -2.5)	0.4	<0.0001	86	0.244
RV S' (cm·s^{-1})	35	1277	2452	0.4	-0.7 (-0.3, -1.1)	0.4	0.001	87	0.452
RV Strain Rate									
RV Free-Wall Strain Rate (s^{-1})	5	116	149	0.04	-0.13 (-0.08, -0.19)	0.6	0.0001	0	0.408
RV Basal Strain Rate (s^{-1})	5	150	287	0.06	-0.26 (-0.06, -0.46)	0.8	0.01	90	0.678
RV Mid Wall Strain Rate (s^{-1})	5	146	271	0.06	-0.10 (-0.24, 0.03)	0.41	0.12	81	0.711
RV Apical Strain Rate (s^{-1})	5	150	287	0.05	-0.02 (0.05, -0.09)	-0.0	0.57	25	0.311

TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; S', peak systolic annular velocity of the right ventricle.

Table 6. Normative reference values for RV pressure, structure, and function.

	Studies *n* (Participants)	Lower Reference Value (95% CI)	Mean (95% CI)	Upper Reference Value (95% CI)
RVSP rest (mmHg)				
Control	21 (1042)	13.3 (12.2 – 14.5)	21.8 (21.0 – 22.6)	30.3 (29.6 – 31)
Athlete	21 (1650)	13.9 (13.0 – 14.8)	24.7 (24.0 – 25.4)	35.5 (34.4 – 36.5)
Reference control				>35 or 36 mmHg
Reference athlete	1 (650)		24	40
RVSP exercise (mmHg)				
Control	8 (234)	26.1 (24.4 – 30.9)	41.7 (38.1 – 45.4)	57.3 (53.3 – 61.2)
Athlete	8 (476)	32.2 (28.7 – 35.6)	52.8 (49.5 – 56.1)	73.4 (67.4 – 79.4)
TAPSE (mm)				
Control	30 (1196)	16.9 (16.4 – 17.4)	23.5 (23.1 – 23.8)	30.1 (29.6 – 30.6)
Athlete	30 (1774)	17.5 (16.9 – 18.1)	25.2 (24.7 – 25.7)	32.9 (32.1 – 33.8)
Reference control	46 (2320)	16 (15 – 18)	23 (22 – 24)	30 (29 – 31)
Reference athlete	1 (650)		2.1	2.6
RV S' (cm·s⁻¹)				
Control (all)	35 (1277)	8.8 (8.4 – 9.2)	12.9 (12.5 – 13.2)	16.9 (16.4 – 17.5)
Male Only	19 (623)	9.3 (8.7 – 9.8)	13.1 (12.6 – 13.7)	17.0 (16.2 – 17.7)
Female Only	10 (453)	8.7 (8.3 – 9.1)	12.6 (12 – 13.2)	16.5 (15.5 – 17.6)
Reference control	43 (2139)	10 (9 – 11)	15 (14 – 15)	19 (18 – 20)
Athlete (all)	35 (2452)	9.2 (8.8 – 9.5)	13.6 (13.3 – 14.0)	18.1 (17.6 – 18.6)
Male Only	19 (1055)	9.5 (8.9 – 10.1)	13.9 (13.4 – 14.4)	18.3 (17.7 – 19.0)
Female Only	10 (1175)	8.6 (8.3 – 8.9)	12.3 (11.6 – 13.1)	16.0 (14.8 – 17.3)
Strain				
RVFWLS (%)				
Control	17 (450)	-20.7 (19.7 – 21.6)	-26.8 (25.1 -28.4)	-32.8 (31.9 – 33.7)
Athlete	17 (605)	-20.1 (19.1 – 21.1)	-26.4 (24.7 – 28.0)	-32.6 (31.5 – 33.7)
RV basal strain (%)				
Control	16 (455)	-17.4 (16.2 – 18.7)	-25.3 (24.5 – 26.1)	-33.2 (31.7 – 34.7)
Athlete	16 (669)	-15.3 (14.1 – 16.6)	-22.9 (22.0 – 23.7)	-30.4 (29.4 – 31.4)
Reference control	5 (183)	-18 (14 – 22)	-28 (25 – 32)	-30 (35 – 43)
RV mid-wall strain (%)				
Control	15 (390)	-20.7 (19.4 – 22.1)	-27.4 (26.4 – 28.4)	-34.1 (32.3 – 35.9)
Athlete	15 (558)	-20.2 (19.0 – 21.5)	-27.3 (26.5 – 28.0)	-34.3 (32.7 – 35.8)
Reference control	4 (125)	-20 (15 – 24)	-29 (25 – 33)	-38 (34 – 43)
RV apical strain (%)				
Control	16 (455)	-20.1 (18.1 – 22.1)	-28.4 (27.0 – 29.8)	-36.7 (35.3 – 38.0)
Athlete	16 (669)	-21.2 (19.5 – 22.9)	-29.3 (28.1 – 30.5)	-37.5 (36.4 – 38.6)
Reference control	4 (145)	-19 (15 – 22)	-29 (26 – 32)	-39 (36 – 43)

Where possible, reference values are provided for controls using the American Society of Echocardiography guidelines (Rudski *et al.*, 2010) using the European Association of Cardiovascular Imaging for athletes (Galderisi *et al.*, 2015). RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; RV S', peak systolic annular velocity of the right ventricle; RVFWLS, right ventricular free wall longitudinal strain.

4.3.4 Meta-Regression and Subgroup Analysis

Sources of heterogeneity were assessed via both linear regression and subgroup analyses. The results from these analyses, however, are observational only and should thus be interpreted with caution. Sex was identified as an important determinant of variation in RV S', with the WMD between athletes and controls being lower in females compared

with males. This was confirmed via both meta-regression ($P = 0.037$) and subgroup analysis ($P = 0.0001$). However, a smaller number of trials and participants contributed to the female subgroup ($n = 5$) than the male subgroup ($n = 17$), meaning that the analysis may not be able to detect subgroup differences. The effects of age, sex and training hours were not significant determinants of variation for any other RV parameter analysed via meta-regression (**Table 7**). However, due to insufficient data availability, it should not be misconstrued that these factors do not influence these RV measures.

The test for subgroup differences indicates that for RV free wall strain, basal strain, mid strain and apical strain there was no statistically significant subgroup effect for sex, training, age and vendor (Error! Reference source not found.; Supplementary Figure 5-8). I^2 remained high across subgroups, therefore subgroup analysis does not explain the heterogeneity in the overall analysis. Furthermore, the I^2 statistic computed for subgroup differences (which describes the percentage of the variability in effect estimates from the different subgroups that is due to genuine subgroup differences rather than sampling error or chance) was also very low. There is a relatively small amount of heterogeneity between results from the studies within the > 35 years of age subgroup (free wall strain, $I^2 = 0\%$; basal strain, $I^2 = 0\%$; mid wall strain, $I^2 = 0\%$; apical strain, $I^2 = 43\%$), although a large degree of variance preserved in the younger subgroup (< 35 years). Similarly, there is a small amount of heterogeneity between studies reporting over 20 hours weekly training volume for apical ($I^2 = 0\%$) and mid wall strain ($I^2 = 0\%$), however there is an uneven covariate distribution which limits the reliability of this finding, with only 2 studies within this subgroup.

The test for subgroup differences indicates that for RVSP there is a statistically significant subgroup effect for sex ($P = 0.0004$), training ($P = 0.0004$), age ($P = 0.03$), suggesting that these covariates do modify the training-induced adaptation. However, for each of these covariates, there is a disproportionate covariate distribution. For example, there are

far more studies (and participants) contributing data to the male (10 studies) and mixed male and female subgroup (10 studies), in comparison to the female subgroup (1 studies). Therefore, it is unlikely that this subgroup analysis can be relied upon to produce valid results. Further, there was a disproportionate covariate distribution for each outcome parameter when divided into subgroups (sex, age, training hours and vendor).

4.3.5 Right Ventricular Structure and Area

RV basal diameter, mid-cavity diameter, and RV length were greater in athletes vs. controls ($P < 0.0001$; **Table 3**). Right ventricular outflow tract (RVOT) dimensions were also significantly greater in athletes. RV end-diastolic and end-systolic areas were also greater in athletes, even when scaled for body surface area. Fractional area change was not significantly different between groups.

Table 7. Meta-regression results for age, sex, training hours and, where possible, strain vendor software for RV functional parameters.

	Age		Sex		Training (hours)		Vendor software	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
RVSP (rest)	-0.13 (-0.33 - 0.07)	0.191	0.46 (-2.18 - 3.10)	0.731	2.22 (-0.33 - 4.77)	0.088		
RVSP (exercise)	-0.84 (-1.84 - 0.15)	0.097	-0.76 (-13.11 - 11.60)	0.905	5.28 (-5.6 - 16.15)	0.342		
TAPSE	0.04 (-0.05 - 0.14)	0.335	-0.54 (-1.46 - 0.38)	0.248	0.15 (-1.16 - 1.45)	0.826		
RV S'	0.04 (-0.01 - 0.08)	0.113	-0.6 (-1.16 - 0.37)	**0.037**	0.80 (-0.05 - 1.66)	0.066		
RV Free-Wall Longitudinal Strain	-0.01 (-0.11 - 0.08)	0.773	0.23 (-0.55 - 1.02)	0.563	-0.58 (-2.45 - 1.29)	0.543	-0.01 (-1.69 - 1.66)	0.987
RV Basal Longitudinal Strain	0.00 (-0.15 - 0.15)	0.991	0.17 (-1.21 - 1.54)	0.815	0.56 (-1.40 - 2.52)	0.577	0.32 (-1.76 - 2.41)	0.762
RV Apical Longitudinal Strain	-0.06 (-0.19 - 0.07)	0.4	0.01 (-1.29 - 1.30)	0.991	-0.66 (-2.03 - 0.70)	0.341	0.11 (-1.79 - 2.01)	0.909
RV Free-Wall Longitudinal Strain Rate	0.01 (-0.01 - 0.02)	0.417	0.04 (-0.08 - 0.15)	0.506	0.04 (-0.07 - 0.16)	0.459		
RV Basal Longitudinal Strain Rate	0.02 (-0.02 - 0.05)	0.411	-0.21 (-0.70 - 0.27)	0.386	-0.01 (-0.04 - 0.02)	0.448		
RV Apical Longitudinal Strain Rate	0.01 (-0.01 - 0.03)	0.39	-0.06 (-0.27 - 0.15)	0.558	-0.01 (-0.04 - 0.03)	0.734		

RV, right ventricle; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; S', peak systolic annular velocity of the right ventricle.

Table 8. Moderator analysis for subgroup effect and potential sources of heterogeneity

	Sex P value	Sex I²	Sex Het. I² P value	Vendor	Vendor P value	Vendor I²	Vendor Het. I² P value	Training	Training P value	Training I²	Training Het. I² P value	Age	Age P value	Age I²	Age Het. I² P value
RV free wall strain *Subgroup*	*0.32*	*11.3*		*Subgroup*	*0.81*	*0*		*Subgroup*	*0.44*	*0*		*Subgroup*	*0.55*	*0*	
Male & Female mix	0.07	64	0.04	**GE**	0.2	63	0.001	**< 15 hrs/wk**	0.02	34	0.16	**<35 yrs of age**	0.28	73	0.0001
Female	0.78	72	0.01	**TomTech**	0.9	73	0.01	**15-19 hrs/wk**	0.47	63	0.04	**>35 yrs of age**	0.76	0	0.59
Male	0.9	59	0.01	**Philips**	NA	NA	NA	**>20 hrs/wk**	0.52	91	0.52				
								Not stated	0.96	0	0.97				
RV basal strain *Subgroup*	*0.35*	*4.7*		*Subgroup*	*0.67*	*0*		*Subgroup*	*0.8*	*0*		*Subgroup*	*0.51*	*0*	
Male & Female mix	0.03	72	0.002	**GE**	0.0001	87	0.00001	**< 15 hrs/wk**	0.0005	71	0.004	**<35 yrs of age**	0.0004	90	0.00001
Female	0.19	87	0.005	**TomTech**	0.11	80	0.03	**15-19 hrs/wk**	0.01	88	0.00001	**>35 yrs of age**	0.0001	0	0.42
Male	0.00001	72	0.002	**Philips**	0.15	NA	NA	**>20 hrs/wk**	0.3	84	0.01				
								Not stated	0.01	69	0.07				
RV mid wall strain *Subgroup*	*0.68*	*0*		*Subgroup*	*0.56*	*0*		*Subgroup*	*0.22*	*31.3*		*Subgroup*	*0.17*	*46.3*	
Male & Female mix	0.87	45	0.12	**GE**	0.72	11	0.34	**< 15 hrs/wk**	0.89	14	0.32	**<35 yrs of age**	0.31	61	0.01
Female	0.42	59	0.0006	**TomTech**	0.53	83	0.01	**15-19 hrs/wk**	0.78	58	0.05	**>35 yrs of age**	0.36	0	0.98
Male	0.45	0	0.59	**Philips**	NA	NA	NA	**>20 hrs/wk**	0.03	0	0.97				
		87						**Not stated**	0.82						
RV apical strain *Subgroup*	*0.81*	*0*		*Subgroup*	*0.39*	*0*		*Subgroup*	*0.72*	*0*		*Subgroup*	*0.18*	*44.1*	
Male & Female mix	0.18	57	0.05	**GE**	0.07	76	0.00001	**< 15 hrs/wk**	0.46	81	0.0001	**<35 yrs of age**	0.38	79	0.00001
Female	0.6	0	0.51	**TomTech**	0.07	0	0.6	**15-19 hrs/wk**	0.05	45	0.1	**>35 yrs of age**	0.01	43	0.12
Male	0.15	73	0.0002	**Philips**	0.8	NA	NA	**>20 hrs/wk**	0.73	0	0.54				
								Not stated	0.48	82	0.02				
RVSP *Subgroup*	*0.004*	*81.7*						*Subgroup*	*0.004*	*77.7*		*Subgroup*	*0.03*	*70.5*	
Male & Female mix	0.002	95	0.00001					**< 15 hrs/wk**	0.01	62	0.0002	**<35 yrs of age**	0.0002	94	0.00001
Female	0.18	NA	NA					**15-19 hrs/wk**	0.0001	98	0.00001	**>35 yrs of age**	0.35	22	0.27
Male	0.004	73	0.0001					**>20 hrs/wk**	0.81			**Not stated**	0.28	NA	NA
								Not stated	0.05	87	0.0001				
TAPSE *Subgroup*	*0.8*	*0*						*Subgroup*	*0.86*	*0*		*Subgroup*	*0.16*	*49.3*	
Male & Female mix	0.009	88	0.00001					**< 15 hrs/wk**	0.03	70	0.0009	**<35 yrs of age**	0.0001	87	0.00001
Female	0.34	93	0.00001					**15-19 hrs/wk**	0.005	91	0.00001	**>35 yrs of age**	0.001	57	0.03
Male	0.00001	87	0.0002					**>20 hrs/wk**	0.0001	29	0.24				
								Not stated	0.07	91	0.00001				
RV S' *Subgroup*	*0.0001*	*88.3*						*Subgroup*	*0.58*	*0*		*Subgroup*	*0.85*	*0*	
Male & Female mix	0.002	80	0.00001					**< 15 hrs/wk**	0.22	84	0.00001	**<35 yrs of age**	0.0003	83	0.00001
Female	0.34	86	0.0001					**15-19 hrs/wk**	0.11	91	0.00001	**>35 yrs of age**	0.25	93	0.00001
Male	0.007	87	0.00001					**>20 hrs/wk**	0.009	89	0.00001				
Not stated	0.00001	NA	NA					**Not stated**	0.07	67	0.02				

RV, right ventricle; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; S', peak systolic annular velocity of the right ventricle.

4.4 Discussion

This meta-analysis of studies reporting RVSP and systolic function indicates that, in comparison to controls, i) athletes demonstrate an elevated resting RVSP, which is further increased (compared to controls) during exercise; ii) measures of RV systolic function, including tricuspid annular displacement and velocity (TAPSE and S'), are greater in athletes. However, iii) athletes demonstrate a similar global and free-wall longitudinal strain but, iv) it is achieved with greater longitudinal strain at the apex and lower strain and strain rate at the base of the RV (**Figure 21**). This meta-analysis provides evidence of region-specific RV adaptation in athletes, which has important implications for future interpretation of physiological and pathological remodelling of the RV.
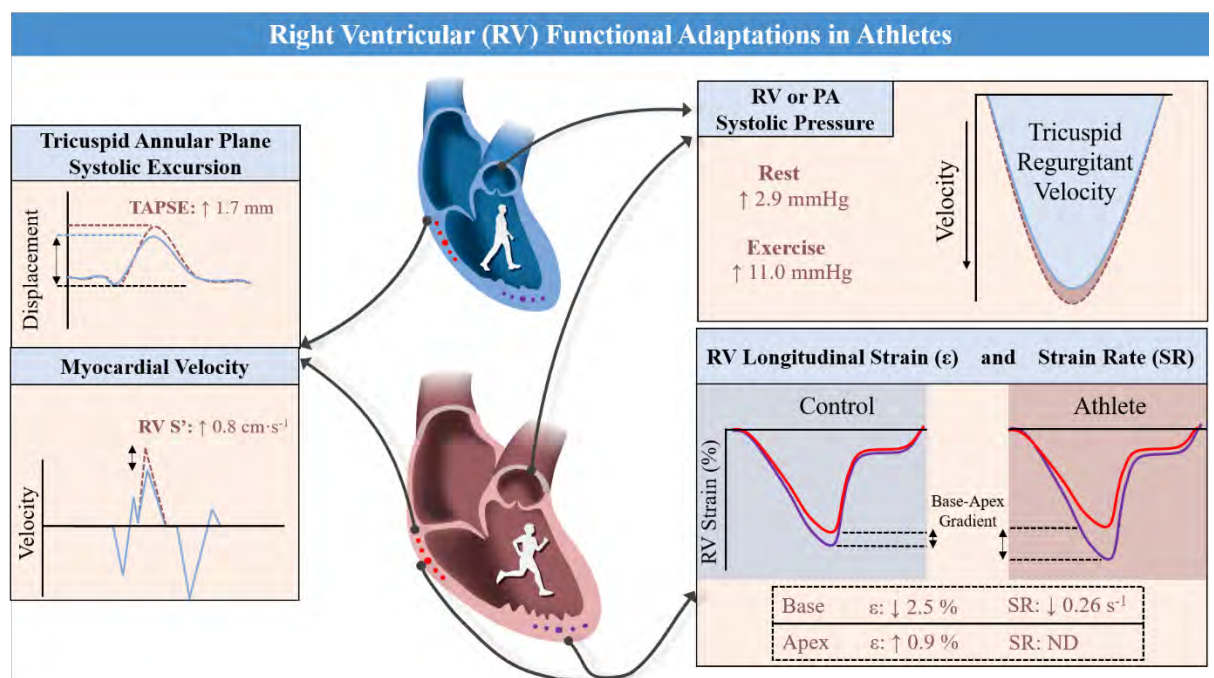
Figure 21. Right ventricular (RV) functional adaptations in endurance athletes.

Values presented are weighted mean difference (WMD) between non-athletic controls and athletes and visually depicted with dashed brown lines. Primary findings include a greater tricuspid annular displacement and myocardial velocity, and region-specific remodelling of the RV free wall, involving a lower strain and strain rate at the base and a greater strain at the apex, in comparison to non-athletic controls. TAPSE, tricuspid annular plane systolic excursion; S', right ventricular systolic myocardial velocity; ε, strain; SR, strain rate; PA, pulmonary artery; ND, no significant difference.

4.4.1 Dynamic Exercise Training is Associated with Elevated Right Ventricular Pressure, Both at Rest and During Exercise

RV ejection of blood and PASP are tightly coupled. As such, it is recognized that a greater SV and pulsatile blood flow increases PASP and upstream RVSP (Pinsky, 2016). However, due to the compliance characteristics of the pulmonary vasculature, the SV contribution to systolic pressure is moderate, with a SV increment of 50 ml suggested to increase systolic pressure by just 4 mmHg in a healthy individual (Harvey *et al.*, 1971). Although, it is plausible that pulmonary vascular adaptations in endurance athletes, as has recently been speculated, mitigate the increased pressures secondary to blood volume expansion (Convertino, 1991) and an elevated SV. Nonetheless, this meta-analysis provides evidence of a consistent elevation in resting RVSP in athletes. As such, athletes may be exposed to elevated RV loading conditions at rest, though the magnitude of the higher pressure is relatively mild. It should be recognized that this analysis highlighted the potential of bias in both resting and exercise RVSP measures. Whilst there are numerous sources of bias which may influence these results, including publication bias (Egger *et al.*, 1997), it is noteworthy that the largest trials that were also blinded for analysis showed significant elevations in RVSP in athletes (D'Andrea *et al.*, 2011). Exercise stresses the pulmonary vasculature due to an increase in cardiac output, SV and left atrial pressures (Wright *et al.*, 2021). Pulmonary vascular resistance decreases during exercise in healthy individuals due to a compensatory increase in cross-sectional area via distention and recruitment of pulmonary vessels (West, 2000). However, since resistance is already low at rest, there is limited capacity to adequately mitigate rising pulmonary artery load. Previous studies have demonstrated the considerable pressure generating capacity of the RV (Wright *et al.*, 2019), which results in a disproportionately greater increase in RV wall stress, in comparison to the LV (La Gerche *et al.*, 2011). In this meta-analysis, RVSP in athletes during moderate-to-intense exercise was consistently elevated beyond that of controls. However, the

relationship between increases in RVSP and cardiac output were similar in both athletes

and nonathletes, as shown in

Table 3. Meta-analysis results comparing the weighted mean difference for right ventricular dimensions and areas between athletes and non-athletic controls.

Parameter	Study n (Participant n Control:Athlete)	MCID 0.2*SDpooled	WMD (95% CI)	Effect size Cohen's d	Z	P value	I2
RV basal diameter (mm)	19 (924:1986)	1.0	-4.7 (-5.9, -3.5)	1.0	7.77	<0.0001	86
RV mid-cavity diameter (mm)	9 (680:1137)	0.9	-5.3 (-6.9, -3.6)	1.1	6.13	<0.0001	91
RV length (mm)	12 (512:818)	1.5	-6.4 (-8.7, -4.1)	0.8	5.42	<0.0001	82
RVOT Proximal PLAX (mm)	7 (380:639)	1.0	-4 (-5, -3)	0.9	6.22	<0.0001	87
RVOT Proximal PSAX (mm)	4 (100:232)	0.9	-3 (-5, -1)	0.7	3.04	0.002	71
RVOT Distal PSAX (mm)	4 (501:884)	1.2	-3 (-3, -2)	0.4	7.26	<0.0001	89
RV EDA (ml)	15 (367:1058)	0.8	-6.5 (-9.9, -3.2)	1.9	3.8	0.0001	98
RV EDA index (ml·m2)	8 (252:303)	0.3	-1.57 (-1.85, -1.28)	0.9	10.8	<0.0001	84
RV ESA (ml)	14 (549:1362)	0.5	-3.5 (-5.4, 1.7)	1.6	3.78	0.0002	97
RV ESA index (ml·m2)	5 (84:105)	0.2	-14.4 (-16.4, -12.5)	0.8	14.47	<0.0001	29
FAC (%)	24 (848:1857)	1.2	0.60 (-0.41, 1.61)	-0.1	1.60	0.25	73

RV, right ventricle; RVOT, right ventricular outflow tract; PLAX, parasternal long axis; PSAX, parasternal short axis; EDA, end-diastolic area; ESA, end-systolic area.

Figure *19*. This finding indicates that RVSP is not altered by training when cardiac output is controlled for, which has previously been evidenced (La Gerche *et al.*, 2010). As such, exercise training involving high cardiac output is associated with both elevated volume and pressure loading conditions for the RV, at rest and during exercise.

4.4.2 Enhanced Right Ventricular Function in Athletes, Assessed via Displacement and Velocity

Structural RV remodelling is well established in endurance athletes. Several reviews have highlighted the frequent observation of ventricular enlargement, dilatation of the ventricular cavity and outflow tract among athletes (D'Andrea *et al.*, 2013; D'Ascenzi *et al.*, 2017*a*), which is further supported by the findings of this meta-analysis (**Table 6**). Region-specific structural adaptation has also been reported, including a 'bulging' of the basal free-wall (Prior & La Gerche, 2012), apical displacement (Brosnan *et al.*, 2015), and apical hypertrabeculation (D'Ascenzi *et al.*, 2017*b*). Relatively fewer investigations, in contrast, have specifically studied the functional adaptation of the athlete's RV. In order to fully understand the extent of RV remodelling it is important that functional adaptation is also considered alongside structural remodelling.

The present meta-analysis provides evidence of a greater basal myocardial longitudinal displacement (TAPSE) at a faster rate (S') in athletes compared with non-athletic controls. These findings, however, may reflect the size and load dependence of these measures of systolic function. LV myocardial velocities derived from tissue Doppler echocardiography, for example, are suggested to be LV length dependent when scaled allometrically (Batterham *et al.*, 2008). As such, observations including greater RV myocardial displacement and velocity in athletes may be considered epiphenomena, secondary to structural remodelling and preload status; however, this requires corroboration with well-designed longitudinal investigation.

4.4.3 Deformation of the Right Ventricle and Region-Specific Remodelling in Athletes

In contrast to displacement and velocity indices of RV systolic function, strain analysis permits the assessment of regional deformation. No difference in 6-segment global longitudinal strain, or 3-segment free-wall longitudinal strain (i.e., inclusion or exclusion of the septum, respectively) was observed between athletes and controls. Unlike myocardial velocities, RV strain measures are relatively less size dependent (Oxborough *et al.*, 2012*b*), which may partly explain the inconsistency between displacement and velocity measurements and deformation-based indices of RV function. Nevertheless, the present meta-analysis provides evidence of a lower RV basal strain in athletes, but a greater reliance on apical strain and therefore greater base-to-apex strain gradient, in comparison to controls. Whilst comparatively fewer studies collected strain rate data, this study reports consistent evidence of lower free-wall and basal RV strain rate. Since there is tight coupling between RV elastance (contractility) and pulmonary arterial elastance (effective arterial load) throughout a range of physiological settings (Tello *et al.*, 2019; Cornwell *et al.*, 2020), it has been suggested that lower RV contractility at rest in athletes may reflect a maintenance of ventricular-arterial coupling, by matching contractility to low afterload (La Gerche *et al.*, 2012*a*). Arterial elastance (calculated as RVSP/SV) may be expected to be lower in athletes in whom SV is far greater but RVSP is only moderately raised. Furthermore, as the basal section contributes most to overall RV volume, less deformation of this segment is required to eject the same volume (Teske *et al.*, 2009; La Gerche *et al.*, 2012*a*), relative to the apex. The mechanisms resulting in training-induced alterations in region-specific function, however, are poorly understood. It is possible that the adapted regional contribution towards longitudinal RV deformation in athletes is a consequence of structural remodelling and/or architectural fibre alignment, altered loading conditions, or intrinsic myocardial cellular and molecular adaptation which is known to occur in other

conditions of chronic haemodynamic load (Voelkel *et al.*, 2006; Addetia *et al.*, 2016). It is possible that these region-specific findings reflect an increased reserve capacity that can be used in situations of high demand, such as exercise, similar to that which has been postulated for the observed reduction in left ventricular torsion in athletes (Nottin *et al.*, 2008). Indeed, La Gerche *et al.* (2012*a*) demonstrated an enhanced contractile reserve of the RV free wallupon exercise. Few studies have assessed RV wall deformation in athletes during exercise (La Gerche *et al.*, 2012*a*; Sanz-de la Garza *et al.*, 2017*a*; Claeys *et al.*, 2020), however characterisation of the RV response to hemodynamic perturbation is crucial to further our understanding of the physiological remodelling associated with the athlete's heart.

Recently, it has been by the European Society of Cardiology, that, from an anatomical perspective, the RV free wall (obtained from an apical four chamber view) could be more appropriately divided into a two-segment model, consisting the RV smooth inlet and the trabeculated body (Badano *et al.*, 2018).In support of this, mid-wall RV longitudinal strain was not significantly different between athletes and non-athletic counterparts in the present study. However, in contrast to these findings, recent study has evidenced a lower mid-wall strain and strain rate in elite pre-adolescent soccer players, whilst basal and apical strain were indifferent (Unnithan *et al.*, 2021). This contradictory finding may highlight a potential phasic regional adaptation to high-dynamic training, initially influencing the relatively 'free' mid-wall segment and later affecting the tethered segments at the base and apex with longer-term of life-long training. Alternatively, RV remodelling during the developmental phase of life may be different to remodelling later in life. Clearly, further study is warranted to explore the potential differences in exercise-induced RV regional remodelling in adults and pre-adolescents.

Whilst potential mechanisms underpinning the lower RV basal strain in athletes have been speculated, explanations for greater apical strain have been comparatively

neglected. Increased trabeculation among well-trained athletes (D'Ascenzi *et al.*, 2017*b*) may introduce imaging artefact at the apex, or may influence deformation characteristics (Paun *et al.*, 2018). Further work is required to clarify the physiological role of trabeculation development. Nonetheless, this meta-analysis provides evidence for a greater apical strain in athletes. Speculative mechanisms that may promote greater apical strain in athletes include, i) altered myofiber architecture and/or ii) heterogenous regional wall stress distribution during haemodynamic load of exercise. It is possible that geometric changes associated with exercise result in an altered myofiber alignment that facilitates greater reliance on apical longitudinal deformation, which may compensate for lower longitudinal deformation at the base. Secondly, on the basis of 'simplified' wall stress assumptions such as the Law of LaPlace, regional differences in RV wall stress may be exacerbated due to RV basal dilatation and increased local radii of curvature with athletic conditioning (Teske *et al.*, 2009). However, due to the crescentic shape of the RV, calculations of wall stress are more complex than the LV and would require information of regional wall thickness and ventricular pressures to appropriately determine regional differences in wall stress. Nonetheless, it is possible that an increased reliance on apical longitudinal deformation in this context results in a more energetically efficient contraction, than an increase in basal deformation would lead to. Ruijsink et al. (2020) have recently proposed that the RV is capable of optimising contractile cost during exercise by ejecting down to a lower ESV, which would be more energetically costly if achieved via the LV. Whilst speculative, it is possible that this also corresponds to the regional mechanics (i.e., elevated base-to-apex strain gradient) by which RV ejection of blood is achieved in athletes, and may contribute towards a contractile reserve (Stewart *et al.*, 2020). Therefore, an elevated base-to-apex longitudinal strain gradient may be considered a hallmark feature of athletic RV functional remodelling that may improve the efficiency of contraction and contribute towards a systolic functional reserve capacity.

4.4.4 Clinical Implications

Differentiating training-induced physiologic RV adaptations from pathologic RV myopathy is clinically important in the care of athletes. RV enlargement is frequently observed in athletes from high-dynamic sporting backgrounds, for which upper reference limits have been identified (Galderisi *et al.*, 2015). In addition to RV enlargement, this study demonstrates altered resting function in athletes, which is dependent on the variable assessed (i.e., myocardial displacement, velocity or deformation) and the region of the RV that is examined. This data supports the implementation of a higher upper reference value for TAPSE (33 mm) beyond that previously recommended in athletes (Galderisi *et al.*, 2015); however, the upper reference value for RV S' is within the upper limits of normal for the general adult population (Rudski *et al.*, 2010). Furthermore, a slightly lower basal longitudinal strain, and an enhanced base-apex strain gradient may be considered normal functional features of the athlete's heart. Notwithstanding, a severe reduction in basal strain (lower reference value < 15%) or a lower functional myocardial reserve during stress testing may warrant further clinical consideration (Claeys *et al.*, 2020). Finally, the upper reference value for RVSP in athletes was 36 mmHg, however 7/21 studies did not consider the influence of right atrial pressure together with the trans-tricuspid pressure gradient. As such, the results from this meta-analysis support the previously recommended upper limit of 40 mmHg for RVSP at rest in athletes (D'Andrea *et al.*, 2011). In summary, clinicians working with athletes can expect to see RV enlargement and elevated pulmonary pressure and should be aware of potential differences in regional function, characterized by a more dynamic apex, a modestly reduced basal longitudinal strain and an augmented base-apex strain gradient.

4.4.5 Limitations and Future Research

While the present meta-analysis offers insight into the region-specific functional adaptation of the athlete's heart, limitations of this study must be acknowledged. Studies that assessed

both males and females were included within this analysis; however, physiological differences between sexes may have influenced these findings. For example, RV strain is consistently elevated in females across all segments (Muraru *et al.*, 2016). Further study is therefore required to identify the specific influence of sex on training-induced functional remodelling of the RV; it is possible that, as with structural remodelling of the LV (Howden *et al.*, 2015), functional adaptation associated with dynamic exercise is diminished in females. Whilst meta-regression did not identify sex as a determinant of variability for RV strain parameters, male dominated studies largely outweighed female studies. Covariate subgroup analysis could not reliably identify between group differences, due to uneven covariate distribution. Furthermore, where there were more proportionally comparable subgroups, subgroup analysis was unable to determine the source of high heterogeneity. Additionally, it must be acknowledged that remodelling is dependent upon volume, intensity, and the type of exercise training. Whilst the current study employed a range of sports involving different exercise doses, sports were categorized based on a predetermined criteria that is routinely used in sports cardiology, which is based upon the hemodynamic profile of the activity (Levine *et al.*, 2015). Rigorous characterization of RV function in strength-trained athletes, however, remains an important area of future work. Furthermore, future studies should assess whether regional measures of RV function regress following a period of detraining, as occurs with RV structure (Pedlar *et al.*, 2018). The high degree of heterogeneity across studies for all parameters should be considered when interpreting the results of this study. Furthermore, the risk of publication bias cannot be neglected, inherent with all meta-analyses, despite statistical interrogation. Additionally, while meta-analyses are useful in defining population central tendency data, in clinical practice it is the outliers who represent the challenge and knowledge of the 'normal' population does not preclude the need for detailed follow-up in these individuals. Finally, WMD were used as the summary statistic, rather than standard mean differences. This decision was made because

each parameter utilised the same scoring system. However, since studies reporting strain were included over an 11-year period (2009 – 2020), it is possible that technological developments over this period may have influenced outcome data. However, this meta-analysis compared the mean difference between two groups from each study, therefore being less influenced by potential absolute differences in outcome parameters between different operating systems. Furthermore, findings were not altered when analysed as standard mean differences (Appendix II, Supplementary Table 2). Utilisation of WMD over standard mean difference also enables easier translation into clinical practice, since standard mean difference is reported in units of standard deviation rather than units of a measurement scale.

4.5 Conclusion

This meta-analysis, based on observational data, shows that athletes may be expected to generate a greater RVSP, both at rest and during exercise, however this relationship appears to be proportional to cardiac output. Furthermore, RV systolic myocardial displacement and velocity at the tricuspid annulus is greater in athletes, in comparison to controls, despite lower myocardial deformation at the base of the RV free-wall and elevated apical deformation. Thus, region-specific adaptations of the RV free-wall, characterized by a widening of the base-to-apex strain gradient, may be considered a normal feature of the athlete's heart. These findings contribute to our understanding of RV remodelling in athletes and highlight the importance of considering RV function in combination with structure in the clinical interpretation of the athlete's heart.

4.6 Study Hypotheses

Null Hypothesis: RV systolic pressure and systolic function are similar in endurance athletes and non-athletic controls (REJECT).

Alternate Hypothesis: An analysis of studies that have assessed RV systolic function in endurance athletes would provide evidence of an elevated RV systolic pressures at rest, and region-specific functional remodelling characterised by a lower basal longitudinal strain and greater apical longitudinal strain, in comparison to non-athletic controls (ACCEPT).

Supplemental Materials: Appendix II

Supplementary Figures 1 – 8

Supplementary Tables 1 – 4

Chapter 5

Evidence of region-specific right ventricular functional adaptation in endurance-trained men in response to an acute volume infusion

Chapter 5. Evidence of region-specific right ventricular functional adaptation in endurance-trained men in response to an acute volume infusion

5.1 Introduction

During dynamic exercise, the healthy RV demonstrates a substantial reserve to maintain ventricular function, despite the elevation in heart rate and RV wall stress (La Gerche *et al.*, 2011; Cornwell *et al.*, 2020). PASP increases with exercise due to a rise in downstream left atrial pressure, and because of the limited capacity for the pulmonary vasculature to further reduce resistance as SV and cardiac output are increased (La Gerche *et al.*, 2010; Kovacs *et al.*, 2012). Pressure generation within the RV (RVSP) is also elevated to drive RV ejection. In **Chapter 4,** it was demonstrated that RVSP was greater in endurance-athletes than in non-athletes, both at rest and during intense exercise, likely as a result of the higher cardiac output achieved at peak exercise. This acute increase in RV load with exercise, coupled with the chronic ~10% blood volume expansion with exercise training, provide a potent stimulus for RV remodelling and an expanded reserve (Convertino, 1991; Sawka *et al.*, 2000), as consistently demonstrated by structural enlargement in endurance athletes (Teske *et al.*, 2009; La Gerche *et al.*, 2012*a*; Oxborough *et al.*, 2012*b*; Arbab-Zadeh *et al.*, 2014).

Owing to the anatomical complexity within the RV, specifically a large cavity dimension at the level of the base which becomes narrower and more trabeculated at the apex (Haddad *et al.*, 2008; Jurcut *et al.*, 2010), regional adaptation to haemodynamic loading with exercise training may disproportionately influence the basal segment. Furthermore, as the basal section contributes most to overall RV volume, less deformation of this segment is required to generate the same SV as that achieved with greater deformation at the apex. This may be particularly true for endurance athletes, in whom RV basal dilatation is common (Teske *et al.*, 2009; Oxborough *et al.*, 2011, 2012*b*). In **Chapter 4**, it was demonstrated that athletes engaged in high-dynamic sports have a lower

myocardial deformation at the RV base, and greater deformation at the apex in comparison to non-athletes. Yet, resting data likely do not reflect the full extent of cardiac remodelling; it is possible that regional RV function, and its response to the repetitive volume load caused by endurance exercise, may also remodel. Moreover, the lower longitudinal deformation at the base of the endurance athlete's RV may reflect an enhanced reserve capacity that may be recruited during states of haemodynamic load, such as exercise, as has been proposed for the lower systolic function in the LV of endurance athletes (Nottin *et al.*, 2008). Given these structural and regional functional adaptations in high-dynamic athletes, as well as the expanded RV reserve required in athletes, the purpose of this study was to examine the RV free wall response to acute plasma volume expansion in endurance-trained and non-trained individuals. It was hypothesised that RV basal deformation would increase to a greater extent in endurance-trained individuals following an increase in circulating volume, in comparison to non-athletic controls.

5.2 Methods

5.2.1 Study Design

Highly trained but non-elite endurance-trained athletes ($n = 13$; ($n = 2$ cyclists, $n = 4$ triathletes and $n = 7$ long-distance runners), engaged with dedicated, structured training programmes, participating in four or more training sessions per week, having done so for 2 or more years) and non-athletic males ($n = 11$) were recruited for this study. Elite athletes were excluded since the experimental intervention (Gelofusine infusion) is considered a doping agent by the World Anti-Doping Association. Average weekly training distance was 46 ± 28 km for runners, 198 ± 88 km for cyclists and 148 ± 58 km for triathletes. The first visit included completion of a health and training questionnaire, anthropometric measurements, resting blood pressure assessment and an incremental cycling test to assess

cardiorespiratory fitness ($\dot{V}O_{2\ peak}$; peak volume of oxygen consumption). During the second visit, echocardiography (two-dimensional, M-Mode, Doppler, and speckle-tracking) data was collected before and immediately after an intravenous Gelofusine infusion (7 ml·kg^{-1}; infused over a 30-minute period) and again following 2 minutes of passive leg elevation to 45°.

5.2.2 Transthoracic Echocardiography: Right Ventricular Imaging

Transthoracic echocardiography and Doppler examinations were performed as described in **Chapter 3.4**. RV end-diastolic area (EDA) and end-systolic area (ESA) were obtained by tracing the endocardial border from 2D images acquired from a RV focused four-chamber apical view. Fractional area change was calculated as the percentage change in RV area from end-diastole to end-systole. From the RV focused four chamber view, linear dimensions were measured at the level of the tricuspid valve (RVD basal), half-way between basal diameter and the apex (RVD mid), and length from the apex to the basal diameter (RVD length). TAPSE was obtained by M-mode, placing the cursor over the RV annulus in the direction of longitudinal excursion in the RV focused view. Systolic RV myocardial velocity (RV S') was obtained via tissue Doppler imaging as outlined in **Chapter 3.4.3.** Speckle tracking derived RV free wall strain was obtained as outlined in **Chapter 3.4.4.**

Systolic pulmonary artery pressure (PASP) was calculated from the tricuspid regurgitant jet using continuous wave Doppler echocardiography. The greatest value obtained from either the RV-focused apical four chamber or parasternal RV inflow view was utilised. For consistency, subsequent measurements were taken from the same imaging window within each participant. The pressure gradient between the right atrium (RA) and RV quantified using the simplified Bernoulli equation ($4V^2$). RVSP was determined by combining the RV-RA pressure difference, with RA pressure estimated as 3 mmHg for all

participants due to the absence of right atrial dilation ($RVSP = 4V^2 + RA$ pressure) (Rudski *et al.*, 2010).

5.2.3 Statistical Analysis

In line with previous recommendations (Oxborough *et al.*, 2012*b*), RV areas and dimensions were scaled allometrically to BSA. Scaling exponents for each measure were derived from the slope of the linear log-log plot of the independent variable (BSA) and the dependent variable (i.e., cardiac parameter of interest). In other words, RV dimensions were individually scaled to BSA raised to the power of the population (endurance and controls combined) *b* exponent. The general allometric equation ($y = a \cdot x^b$) was used and linearised by taking the natural logarithms of both sides of the equation: $\log Y = \log a + b \log X$. exponent 'b' is simply the slope of the linear log-log plot, proportionality coefficient 'a' is calculated as the antilog of the Y-intercept term. Baseline participant characteristics were analysed using an independent samples t-test. The changes in haemodynamic and RV structural and functional measurements that followed infusion and passive leg-raise were expressed as percent change of the mean values at baseline. A two-way mixed measures analysis of covariance was conducted between group (endurance-trained vs. controls) and loading condition (post-infusion and passive leg-raise). Age was considered a covariate due to the significant difference between groups and the potentially important influence for key RV parameters. Where a significant main effect was observed, data were analysed for simple main effects using Sidak's adjustment for multiple comparisons. To determine whether meaningful differences were present, effect sizes (Cohen's *d*) are reported. Data were expressed as mean ± standard deviation (SD) and a *P* value < 0.05 was considered significant.

5.3 Results

5.3.1 Participant Characteristics and Resting Right Ventricular Structure and Function

By design, cardiorespiratory fitness ($\dot{V}O_{2peak}$) was higher in the endurance-trained group in comparison to controls ($P < 0.001$). As shown in **Table 9**, resting heart rate was significantly lower in endurance-trained compared with controls ($P = 0.001$); however, no differences were observed in resting systolic ($P = 0.264$) or diastolic blood pressure ($P = 0.621$).

Table 9. Baseline participant characteristics including training-status, and measures of haemodynamic and right ventricular structure and function.

	Controls (*n* = 11)	Endurance-trained (*n* = 13)	t-test (*P* value)
Demographics			
Age (years)	24 ± 4 (21 − 26)	28 ± 5 (26 − 31)	**0.017**
Height (cm)	179 ± 9 (174 − 185)	181 ± 6 (178 − 184)	0.531
Body mass (kg)	76 ± 8 (71 − 81)	75 ± 6 (72 − 79)	0.872
Body surface area (m^2)	1.94 ± 0.12 (1.87 − 2.02)	1.95 ± 0.10 (1.90 − 2.01)	0.826
$\dot{V}O_{2\,peak}$ (ml·kg^{-1}·min^{-1})	40 ± 5 (38 − 43)	55 ± 9 (50 − 60)	**< 0.001**
$\dot{V}O_{2\,peak}$ (ml·min^{-1})	3042 ± 276 (2879 − 3205)	4082 ± 519 (3799 − 4364)	**< 0.001**
Training (Years)		5 ± 2	
Training Frequency (sessions/wk)	1 ± 1	7 ± 2	**< 0.001**
Haemodynamic			
Heart Rate (beats·min^{-1})	59 ± 7 (55 − 62)	50 ± 6 (47 − 53)	**< 0.001**
Systolic BP (mmHg)	118 ± 6 (114 − 122)	122 ± 8 (117 − 126)	0.262
Diastolic BP (mmHg)	72 ± 7 (68 − 76)	71 ± 6 (68 − 74)	0.621

Data presented as mean ± SD (confidence intervals). $\dot{V}O_{2\,peak}$, peak volume of oxygen consumption per minute. BP, blood pressure.

Scaled and absolute RV areas were significantly greater in the endurance-trained individuals compared with controls, but RV fractional area change was not significantly different (**Table 10**). Absolute and scaled RV basal diameter and RV length were greater in the endurance-trained group ($P < 0.05$). RVD mid-cavity dimension was greater in endurance-trained individuals although not reaching statistical significance (P = 0.065).

RVSP was similar between groups ($P = 0.311$). TAPSE was greater in the endurance-trained group, although not reaching conventional statistical significance ($P = 0.054$), although other measures of RV function including RV S' and RV free wall longitudinal and regional strain (**Table 10**) and SR, were not significantly different between endurance-trained individuals and controls at rest.

Table 10. Baseline right ventricular structure and function in controls and endurance-trained individuals.

	Controls ($n = 11$)	Endurance-trained ($n = 13$)	t-test (P value)
RV Structure			
RV end-diastolic area (cm^2)	22.6 ± 2.6 (21.0 – 24.1)	26.2 ± 4.7 (23.6 – 28.7)	**0.017**
RV end-systolic area (cm^2)	10.9 ± 1.9 (9.8 – 12.0)	13.2 ± 2.5 (11.8 – 14.5)	**0.012**
Scaled RV end-diastolic area (cm·m^2)$^{0.604}$	15.1 ± 1.9 (14.0 – 16.3)	17.4 ± 2.9 (15.8 – 19.0)	**0.026**
Scaled RV end-systolic area (cm·m^2)$^{0.381}$	8.5 ± 1.6 (7.5 – 9.4)	10.2 ± 1.8 (9.2 – 11.2)	**0.023**
RV FAC (%)	51 ± 5 (48 – 55)	49 ± 6 (46 – 52)	0.321
RVD basal (mm)	38 ± 3 (36 – 40)	42 ± 4 (40 – 44)	0.004
RVD mid (mm)	25 ± 2 (24 – 27)	28 ± 4 (25 – 30)	0.065
RVD length (mm)	82 ± 4 (80 – 84)	89 ± 8 (85 – 94)	0.056
Scaled RVD basal (mm·m^2)$^{0.488}$	28 ± 2 (26 – 29)	31 ± 3 (29 – 32)	**0.016**
Scaled RVD mid (mm·m^2)$^{0.245}$	21 ± 2 (20 – 23)	23 ± 3 (22 – 25)	0.064
Scaled RVD length (mm·m^2)$^{0.548}$	65 ± 3 (63 – 67)	70 ± 6 (67 – 73)	**0.006**
RV Function			
TAPSE (mm)	22.5 ± 1.9 (21.4 – 23.7)	24.2 ± 4.7 (22.5 – 27.6)	0.054
RV S'	0.15 ± 0.02 (0.14 – 0.16)	0.15 ± 0.03 (0.13 – 0.17)	0.422
RVSP (mmHg)	19.4 ± 4.3 (16.9 – 22.0)	20.3 ± 4.2 (18.0 – 22.6)	0.311
Total RV free wall strain (%)	25.4 ± 2.9 (25.1 – 27.5)	26.3 ± 2.2 (25.1 – 27.5)	0.202
Basal RV strain (%)	21.9 ± 3.6 (19.8 – 24.1)	21.2 ± 3.5 (19.3 – 23.1)	0.300
Mid wall RV strain (%)	28.8 ± 3.1 (27.2 – 30.5)	30.5 ± 4.8 (28.1 – 32.9)	0.165
Apical RV strain (%)	25.4 ± 4.7 (22.6 – 28.1)	26.8 ± 3.6 (24.8 ± 28.7)	0.211
RV base-to-apex strain gradient (%)	3.4 ± 5.8 (0.0 – 6.8)	5.8 ± 5.7 (2.7 – 8.9)	0.166
Total RV free wall strain rate (%/s)	1.45 ± 0.31 (1.27 – 1.64)	1.42 ± 0.09 (1.37 – 1.47)	0.345
Basal RV strain rate (%/s)	1.37 ± 0.39 (1.14 – 1.60)	1.18 ± 0.24 (1.05 – 1.31)	0.081
Mid wall RV strain rate (%/s)	1.52 ± 0.27 (1.37 – 1.66)	1.55 ± 0.25 (1.42 – 1.67)	0.392
Apical RV strain rate (%/s)	1.47 ± 0.39 (1.24 – 1.71)	1.53 ± 0.33 (1.35 – 1.71)	0.357

Data presented as mean ± SD (confidence intervals). RVD, right ventricular dimension; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; RVSP, right ventricular systolic pressure. Data presented as mean ± SD (confidence intervals). Scaling exponents (β) for body surface area are presented alongside relevant parameters as: (unit)^β.

5.3.2 Blood Volume and Haemodynamic Effect of Volume Loading

There were no statistically significant differences in the total infusion volume (531 ± 47 ml vs. 533 ± 58 ml, endurance vs. control respectively, $P = 0.928$; $d = 0.04$) or the estimated percentage change in blood volume pre-post infusion between the groups ($12 \pm 4\%$ vs. $13 \pm 4\%$, endurance-trained vs. control respectively; $P = 0.867$; $d = 0.14$). Brachial blood pressure remained similar between groups. RVSP increased in both endurance-trained and controls ($\Delta 3.6 \pm 3.2$ mmHg, $P < 0.001$) following Gelofusine infusion and PLR.

5.3.3 Effects of Plasma Volume Expansion on Right Ventricular Function in the Trained and Untrained Heart

RV areas and structural dimensions increased to a similar extent in endurance-trained individuals and controls post-infusion and passive leg raise (**Table 10**). The increase in global functional measures including TAPSE, RV S' and RV free wall longitudinal strain were also similar between groups at both time-points (**Table 11**). However, as shown in **Figure 22**, the endurance-trained group displayed a significant increase in RV basal longitudinal strain which was greater than that of controls (ANCOVA $P = 0.041$) in response to Gelofusine infusion plus passive leg raise ($P = 0.043$; $d = 0.72$), although failing to reach statistical significance with Gelofusine infusion alone ($P = 0.074$; $d = 0.89$). Free-wall, basal, mid wall and apical SR remained similar between groups following both infusion and passive leg-raise.

Table 11. Percent change in RV variables from baseline in response to 7 ml·kg^{-1} intravenous Gelofusine infusion and subsequent passive leg raise (age adjusted mean ± SE)

Variable, %	Infusion		Passive Leg Raise		ANCOVA (*P* value) Between effects
	Controls	Endurance-trained	Controls	Endurance-trained	
RVSP (adjusted)	27 ± 6	14 ± 6	30 ± 8	18 ± 7	0.216
RVD Base (adjusted)	3 ± 3	2 ± 2	4 ± 3	4 ± 2	0.909
RVD mid-wall (adjusted)	1 ± 4	6 ± 4	1 ± 4	5 ± 3	0.292
RVD length (adjusted)	2 ± 1	3 ± 1	2 ± 1	4 ± 1	0.480
RV area diastole (adjusted)	5 ±5	9 ± 4	4 ± 4	8 ± 4	0.528
RV area systole (adjusted)	8 ± 7	9 ± 6	5 ± 5	8 ± 4	0.819
RV FAC (adjusted)	0 ± 4	3 ± 4	0 ± 4	3 ± 4	0.632
RV S' (adjusted)	10 ± 10	8 ± 8	10 ± 8	11 ±7	0.216
TAPSE (adjusted)	8 ± 3	5 ± 2	7 ± 3	7 ± 3	0.737
RV 6 segment Global Longitudinal Strain (adjusted)	9 ± 3	5 ± 3	7 ± 3	4 ± 3	0.436
Total RV free wall strain (adjusted)	7 ± 3	7 ± 3	4 ± 3	7 ± 3	0.793
Basal RV strain (adjusted)	5 ± 5	18 ± 4	1 ± 5	18 ± 4*	**0.041**
Mid wall RV strain (adjusted)	6 ± 4	4 ± 4	4 ± 4	3 ± 4	**0.758**
Apical RV strain (adjusted)	11 ± 5	4 ± 4	10 ± 5	5 ± 5	0.404
RV 6 segment global longitudinal strain rate (adjusted)	9 ± 3	6 ± 3	7 ± 3	4 ± 3	0.436
Total RV free wall strain rate	7 ± 3	7 ± 3	5 ± 3	6 ± 3	0.996
Basal RV strain rate	-2 ± 8	7 ± 7	-3 ± 7	8 ± 6	0.322
Mid wall RV strain rate	5 ± 6	-1 ± 5	1 ± 6	2 ± 6	0.777
Apical RV strain rate	7 ± 10	13 ± 9	-2 ± 9	41 ± 8	0.589

* *P* < 0.05 significant difference between groups (simple main effects using Sidak's adjustment for multiple comparisons. RVSP, right ventricular systolic pressure; RV, right ventricle; RVD, right ventricular diameter; FAC, fractional area change; S', systolic myocardial velocity; TAPSE, tricuspid annular plane systolic excursion; GLS, global (6-segment) longitudinal strain; GLSR, global longitudinal strain rate; RVFWSL, right ventricular free-wall longitudinal strain; RVFW SR, right ventricular free-wall longitudinal strain rate.
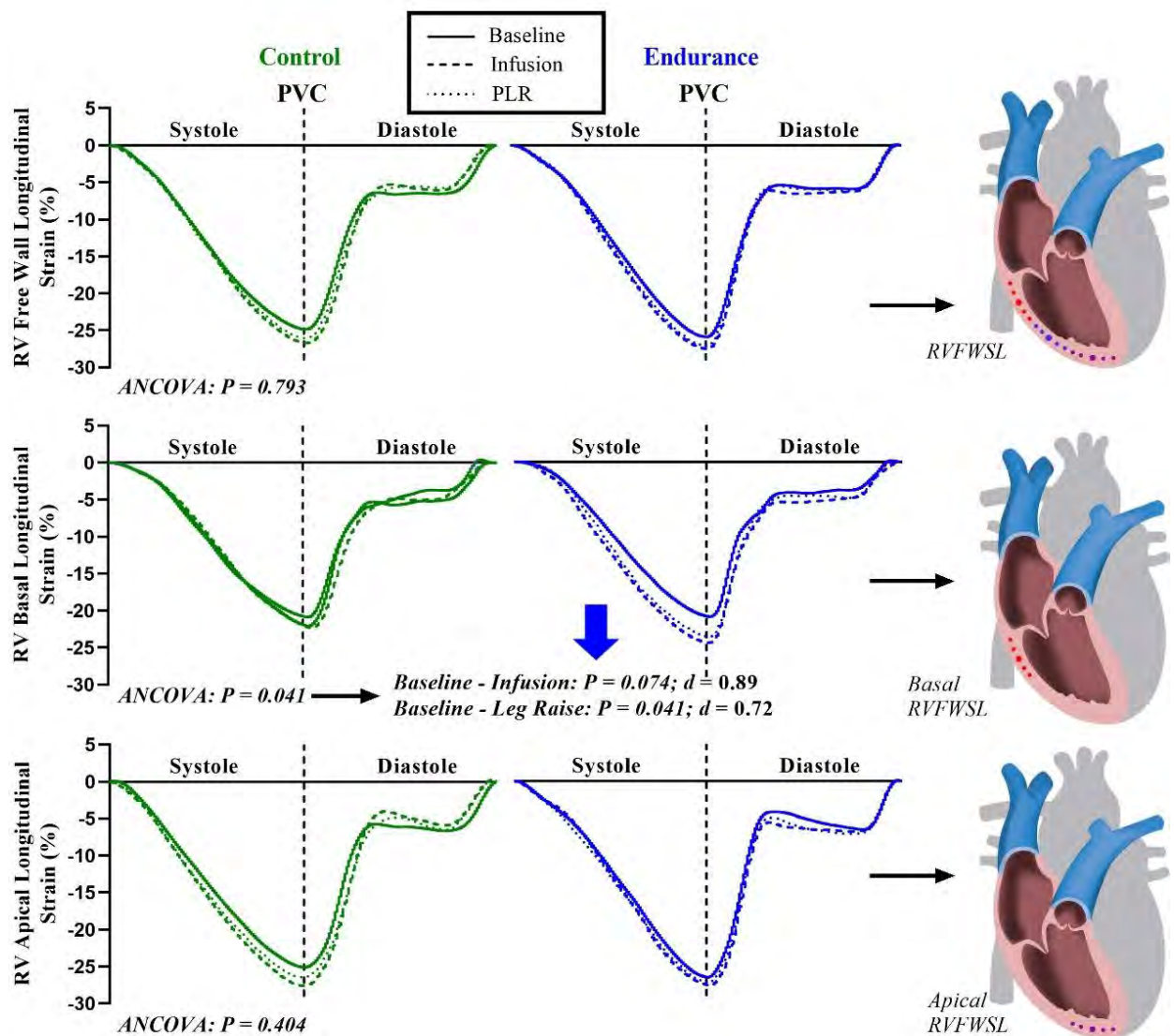
Figure 22. Right ventricular free wall strain (RV FWSL) among endurance-trained (right panel) and control participants (left panel) before (solid line) and after 7 ml·kg⁻¹ intravenous Gelofusine infusion (dashed line) and subsequent passive leg-raise (PLR; dotted line).

Blue arrow illustrates statistical significance of between-subjects effects, as assessed from a two-way analysis of covariance of the delta (%), accounting for age. Cohen's d effect sizes also reported.

5.4 Discussion

To my knowledge, this is the first study to assess regional functional adaptation in endurance-trained individuals, in response to intravenous infusion, designed to evoke a distinct haemodynamic volume (preload) stimulus on the RV. The primary findings of this study are that, in line with the hypothesis and despite comparable RV free-wall longitudinal strain at rest, longitudinal deformation at the base of the RV was augmented in the endurance-trained group beyond that of non-athletic controls when challenged with an acute volume infusion. This finding suggests that the RV phenotype associated with endurance training is not simply characterised by differences in resting structure and function, which may conceal an enhanced functional reserve capacity, but also by differences in regional *function* in response to increased circulating volume.

5.4.1 Global Right Ventricular Response to Plasma Volume Expansion in the Endurance-Trained Heart

In the present study, consistent with the athlete's heart phenotype (Oxborough *et al.*, 2012*b*; La Gerche *et al.*, 2012*b*), endurance-trained individuals had larger RV areas and basal diameters, lower resting heart rates. Consistent with the results of **Chapter 4**, despite mild RV enlargement and enhanced displacement of the tricuspid annulus (TAPSE), no differences in free-wall longitudinal deformation were found between endurance-trained individuals and controls at rest. Furthermore, as has been previously observed in response to exercise (La Gerche *et al.*, 2012*a*), free-wall longitudinal deformation, displacement, and velocity increased in both endurance-trained and control groups by a similar extent in response to acute plasma volume expansion. In contrast to the findings of **Chapter 4**, RV pressure generation was not different between endurance-trained and nonathletic counterparts; nonetheless, the increase in RVSP in response to plasma volume expansion was similar between groups. Variability in RVSP in this cohort and others may be due to differences in downstream left atrial pressure (Tedford *et al.*, 2012; Kovacs *et al.*, 2012;

Wright *et al.*, 2021), and perhaps a training effect on pulmonary blood volume or pulmonary vascular distensibility (Lalande *et al.*, 2012; Tedjasaputra *et al.*, 2016), although these speculations require further mechanistic investigation.

5.4.2 Regional Right Ventricular Myocardial Response to Plasma Volume Expansion in the Endurance-Trained Heart

Morphological differences between the base and the trabeculated apex, including myofiber alignment, local radii of curvature, and relative dimensions, may promote a basal portion of the RV that is exposed to greater increases in wall stress during exercise (Teske *et al.*, 2009). These differences may promote preferential dilation of the basal segment, and subsequently reduced strain (Teske *et al.*, 2009). Elevated preload conditions at rest, due to significant blood volume expansion (Convertino, 1991), may also partially explain the lower RV basal deformation in athletes. For example, mathematical modelling studies of the LV predict that peak longitudinal strain will decrease with increasing ventricular size; the contribution of preload or ventricular size likely relates to fibre orientation and relative contribution of the Frank-Starling mechanism, which may be different at different regions of the RV. This decrement in deformation at the base may be sufficient to produce a SV that is adequate at rest but allows a greater reserve capacity to be utilised during exercise. In contrast to prior investigations summarised in **Chapter 4**, and despite mild RV basal dilatation among endurance-trained individuals, no difference was observed in apical or basal RV free wall deformation at rest in comparison non-athletes. It is possible that differences in athletic status may be responsible for the contradictory findings in this study in comparison to **Chapter 4**. Teske et al. (2009) for example, demonstrated a significantly lower speckle tracking derived RV basal strain in elite athletes (Olympic and internationally competing professional endurance athletes) training 24.2 h/week in comparison to non-athletes; however, this distinction was not found in non-elite athletes, despite a significant training volume of 12.5 h/week. Athletes recruited for the present study were well-trained

(training 7 ± 2 times per week for 5 ± 2 years; 55 ± 9 ml·kg^{-1}·min^{-1}), but non-elite, and therefore the magnitude of difference in regional strain parameters may be diminished between endurance athletes and controls, perhaps due to a dose-dependent adaptation.

Following acute artificial plasma volume expansion, in line with the hypothesis, RV basal strain was augmented beyond that of non-athletic controls, whilst the magnitude of increase in apical strain was similar between groups. Prior observation of a lower RV basal strain in athletes (**Chapter 4**) therefore, is unlikely to be related to an enhanced blood volume but may reflect remodelling of the myocardium. This is consistent with the proposed mechanistic role in which plasma volume expansion has on LV adaptation in initial phase of training, which is unlikely to substantially contribute to remodelling with extended training (Weiner & Baggish, 2014). As such, the temporal progression of exercise induced remodelling of the RV, with consideration of region-specific adaptation, should be considered in future work.

Since the smooth inlet at the base and trabecular portions at the apex have a different muscular arrangement (Jurcut *et al.*, 2010), the adaptation to haemodynamic stress associated with exercise may also differ. In support of this, it is recognised that endurance training can result in hypertrabeculation of the apex and dilatation of the base (D'Ascenzi *et al.*, 2017*b*). Preferential deformation at the base of the RV in response to acute plasma volume expansion, therefore, may arise as an epiphenomenon associated with exercise-induced structural adaptations. Alternatively, the observed functional differences may reflect a reserve capacity that may be engaged during exercise. Indeed, La Gerche et al, (2012*a*) have demonstrated the normal contractile reserve of the RV free wall segments in athletes during exercise.

In concert with the findings of **Chapter 4**, mid-wall RV longitudinal strain was not significantly different between endurance-trained individuals at rest and remained similar

following haemodynamic perturbation. Whilst it was not expected that the mid-wall would respond differently in adult athletes in this study, recent cross-sectional investigation has demonstrated a lower mid-wall strain in pre-adolescent soccer players (Unnithan *et al.*, 2021). As such, it is possible that the exercise-induced regional remodelling process is different during pre-adolescence than that which occurs during adulthood. This remains speculative and deserving of further investigation.

This model of haemodynamic perturbation, simulating the blood volume expansion that follows prolonged endurance exercise, highlights the potential regional specificity of exercise induced functional adaptation. Clinical models of chronic pressure overload have also demonstrated a divergent structural and functional adaptation of the base and apex of the RV, resulting in region-specific alterations in myocardial deformation (Dambrauskaite *et al.*, 2007; Bodhey *et al.*, 2008). Dambrauskaite et al. (2007) found that apical deformation was significantly lower than the basal region in a pressure overloaded RV in patients with pulmonary hypertension. These findings suggest that chronic adaptation to haemodynamic load may differ between regions of the RV and support the finding of regional functional adaptation in endurance-trained individuals.

Assessment of the functional RV response is crucial to improving our understanding of exercise-induced RV remodelling. While RV functional reserve across the RV free-wall may be comparable between athletes and non-athletes (La Gerche *et al.*, 2012*a*), this study demonstrates that, in endurance-trained individuals, the increase in myocardial deformation at the base of the RV free wall is greater in response to an increase in circulating volume, similar to that which follows exercise. Endurance type exercise is associated with an increase in preload, afterload and contractility (La Gerche *et al.*, 2017; Cornwell *et al.*, 2020). Following prolonged exercise, however, there is a circulatory blood volume expansion (Sawka *et al.*, 2000), which may evoke an isolated post-exercise stimulus for RV remodelling. As the novel findings of this study highlight, the RV of endurance-trained

individuals appears to develop a distinct regional adaptation in response to an isolated volume stimulus, which may facilitate or optimise the ejection of blood from the RV when preload is a major stimulus, for example during exercise. As such, the athletic heart phenotype of endurance athletes may be extended to incorporate a region-specific *functional* response to a haemodynamic volume stimulus. Furthermore, utilisation of an intravenous infusion to evoke a haemodynamic challenge for the RV may represent a novel, practical solution study the RV without substantially jeopardising image quality, which often occurs during stress-testing involving exercise, owing to the high heart rates, respiratory artefact and limb movement.

5.4.3 Clinical Perspective

The diagnostic importance of sensitive measures of myocardial function, such as deformation imaging, has been established for the differentiation of arrhythmogenic cardiomyopathy (Mast *et al.*, 2019; Claeys *et al.*, 2020). Abnormal deformation, particularly a lower deformation of the RV basal area, may help to discriminate early "subclinical stage" arrhythmogenic cardiomyopathy that is not detected by conventional approaches (Mast et al., 2019). Differentiation between arrhythmogenic cardiomyopathy and normal physiologic remodelling with athletic training remains an extremely important consideration for sports cardiologists, due to the considerable morphologic overlap (Claeys *et al.*, 2020). It is intriguing that, as has been demonstrated in **Chapter 4**, basal RV free wall strain is also lower in endurance-trained athletes. However, data from the present study suggest perturbation of haemodynamic load unmasks a functional reserve of the basal RV segment, which is enhanced in comparison to non-athletic controls.

5.4.4 Study Limitations

This study is limited by the exclusion of competitive athletes, as intravenous Gelofusine infusion is considered a prohibited substance by the World Anti-Doping Agency. Those performing the greatest training load may have the most pronounced remodelling and greatest change in resting strain and strain rate in comparison to controls and non-elite athletes (Teske *et al.*, 2009). Whilst elite athletes were not included, trained individuals were performing a substantial volume of training, and had a cardiorespiratory fitness similar to other studies investigating RV myocardial mechanics in athletes (La Gerche *et al.*, 2015). Additionally, endurance athletes were slightly older than controls, by approximately 4 years, however this was controlled for by incorporating age as a covariate in statistical analyses. Whilst ageing is associated with a reduction in longitudinal myocardial function and deformation (Chung *et al.*, 2004; Innelli *et al.*, 2009; Alcidi *et al.*, 2018) a slight difference in age of less than 5 years is unlikely to significantly alter the findings of this study. In accordance with recent task force consensus (Badano *et al.*, 2018), longitudinal strain of the RV free-wall is reported. However, it is recognised that regional shortening of the septum contributes to the ejection phase of the RV (Buckberg & Hoffman, 2014). Nonetheless, the same findings were observed for global RV strain (i.e., 6-segment strain including free-wall and septum; **Table 11**). Finally, specific studies to examine the female athlete's heart are warranted and are currently being undertaken (Sanz-de la Garza *et al.*, 2017*a*; Williams *et al.*, 2017; Lakatos *et al.*, 2018).

Resistance athletes were not included in this study since, as discussed in **Chapter 2.6.3**, resistance exercise is unlikely to elicit a meaningful increase RV wall stress. Pulmonary artery pressure is unlikely to be directly altered by resistance exercise, whilst venous return is attenuated (Alegret *et al.*, 2015). In contrast, the LV may be exposed to a considerable increase in systemic pressure during resistance exercise (MacDougall *et al.*,

1985, 1992). Functional remodelling of the LV in resistance athletes, therefore, requires attention and will be addressed in the next chapter (**Chapter 6**).

5.5 Conclusion

This model of acute haemodynamic perturbation highlights the potential regional specificity of exercise induced functional adaptations within the RV. Therefore, the RV phenotype associated with endurance training is not simply characterised by differences in resting structure and function, but also by a region-specific *functional response* to changes in circulating volume, most prominent at the base of the RV free wall.

5.6 Study Hypotheses

Null Hypothesis: The RV functional response to an increase in circulating volume would not be different between endurance-trained individuals or nonathletic controls (REJECT).

Alternate Hypothesis: Endurance training would be associated with a functional RV response to a change in haemodynamic load, which would be characterised by a region-specific increase in basal longitudinal strain (ACCEPT).

Supplemental Materials: Appendix III

Supplementary Table – 7 - 8

Chapter 6

Stimulus-specific functional remodelling of the left ventricle in endurance and resistance-trained men

Chapter 6. Stimulus-specific functional remodelling of the left ventricle in endurance and resistance-trained men

A version of this thesis chapter has been published in the

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(Appendix VIII)

6.1 Introduction

The theoretical framework for dichotomous structural remodelling of the LV in response to repetitive hemodynamic pressure or volume overload caused by resistance or endurance based athletic-training was first suggested by Morganroth et al. (1975). Despite this hypothesis being proposed over 45 years ago, our understanding of the athlete's heart has been based largely upon the resting assessment of LV structure in highly trained athletes. However, there is growing acceptance that most sport disciplines likely convey a mixed hemodynamic stimulus involving an acute increase in both pressure and volume loading (Utomi *et al.*, 2013; Haykowsky *et al.*, 2018). Even so, athletes who demonstrate marked structural adaptations (e.g., increased LV wall thickness, cavity size and relative wall thickness) (Pelliccia *et al.*, 1991, 1999) may also exhibit divergent changes in resting LV function. Several reports indicate that endurance training results in enhanced LV diastolic

function (Levy *et al.*, 1993; Baggish *et al.*, 2008*a*), possibly due to alterations in blood volume (Coyle *et al.*, 1986), chamber compliance (Levine *et al.*, 1991), pericardial remodelling (Kroeker *et al.*, 2003; Esch *et al.*, 2007) and/or underlying cellular adaptation (Melo *et al.*, 2018; Domańska-Senderowska *et al.*, 2019). Conversely, strength training has been shown to reduce diastolic function at rest, perhaps due to a reduction in LV compliance resulting from concentric hypertrophy (Baggish *et al.*, 2008*a*; Mihl *et al.*, 2008). However, greater wall thicknesses in highly trained resistance athletes, and or those with underlying hypertension, may enhance the heart's ability to maintain SV when arterial pressure is elevated (Shave *et al.*, 2019).

Analogous to skeletal muscle (van Wessel *et al.*, 2010), even in the absence of structural remodelling, it is possible that chronic exercise training may result in training-specific adaptations in the LV functional response to changes in haemodynamic load. Indeed, **Chapter 5** demonstrates the RV myocardial functional adaptation in endurance-trained athletes to increased haemodynamic volume load. Evaluation of LV longitudinal strain (i.e., myocardial deformation) characteristics alongside conventional volumetric measurements provides the opportunity to simultaneously examine functional LV remodelling and the mechanisms that may explain potential training-specific adaptations. In highly trained (engaged with dedicated, structured training programmes, participating in four or more training sessions per week, having done so for 2 or more years), but non-elite, endurance and resistance-trained males and non-athletic controls, this study sought to compare the LV response to (i) isometric leg-press exercise (i.e., pressure load) and (ii) an intravenous Gelofusine volume infusion with and without passive leg-raise (i.e., progressive volume load). It was hypothesized that athletic training would be associated with training-specific adaptation in the LV functional response to a change in load. This would be characterized by a maintenance of SV in resistance-trained individuals in response to isometric exercise, and an augmented SV in endurance-trained individuals

when challenged with an increased circulating volume. To investigate the mechanisms responsible for potential training-specific functional remodelling, a secondary exploratory analysis was conducted to examine changes in LV longitudinal myocardial deformation characteristics in the three groups.

6.2 Methods

6.2.1 Study Participants

Highly trained but non-elite (athletes engaged with dedicated, structured training programmes, participating in four or more training sessions per week, having done so for 2 or more years) endurance-trained ($n = 15$; ($n = 2$ cyclists, $n = 5$ triathletes and $n = 8$ long-distance runners)), resistance-trained ($n = 14$; ($n = 2$ natural body builders, $n = 5$ weight lifters and $n = 7$ non-specific resistance athletes (i.e., gym goers)) and non-athletic males ($n = 13$) were recruited to participate in this study. Of the endurance-trained cohort, average weekly training distance was 44 km for runners, 198 km for cyclists and 158 km for triathletes. All resistance-trained men exclusively performed moderate to high-intensity full-body resistance training programs and did not engage in any aerobic exercise. Due to the experimental procedures involving intravenous volume infusion, competitive athletes subject to doping regulations were unable to be recruited; Gelofusine is listed as a banned substance by the UK and world anti-doping agencies, as it can act as a potential masking agent.

6.2.2 Study Design

Participants were assessed on three separate visits, outlined in further detail in **Chapter 3**. The first testing session involved the completion of a health and training questionnaire, anthropometric measurements, resting blood pressure measurement, and the assessment of a seated leg-press one-repetition maximum (1RM). After a minimum of 30-minutes recovery, to assess cardiorespiratory fitness ($\dot{V}O_2$ peak; peak volume of oxygen

consumption), an incremental cycling test was completed. The subsequent experimental visit involved either a pressure load or a volume load, with the final visit involving the second experimental condition. During the pressure loading visit, transthoracic echocardiographic measurements were obtained at rest and during isometric leg-press exercise at 20%, 40% and 60% 1RM, respectively. The volume loading condition involved a resting echocardiogram before and immediately after an intravenous Gelofusine infusion (7 ml·kg^{-1}; infused over a 30-minute period) and again following a 2-minute passive leg elevation to 45° (**Figure 23**).
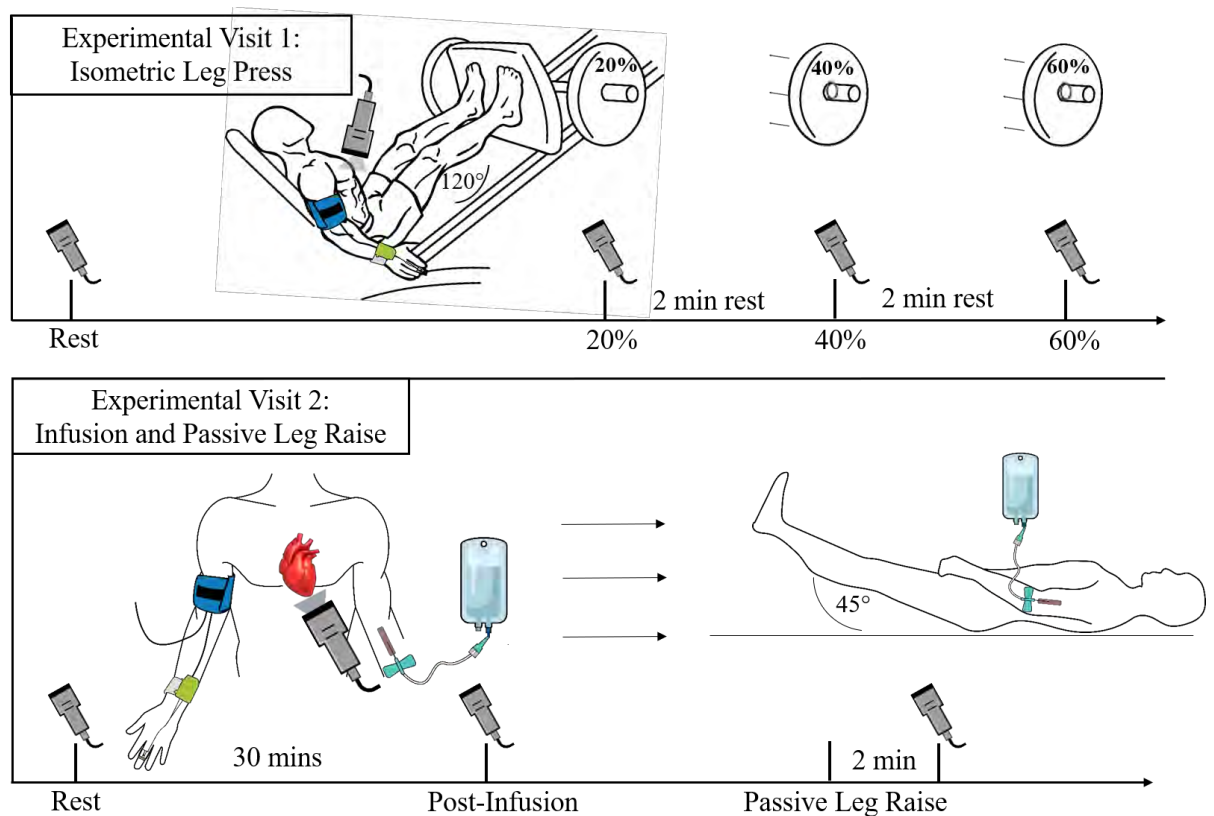
Figure 23. Schematic of the experimental protocol.

Non-athletic controls, endurance-trained men and resistance-trained men performed isometric leg-press exercise at 20%, 40% and 60% of one repetition maximum (1RM). Transthoracic echocardiography (indicated by ultrasound probe) was undergone at rest and during 1-2 minutes of exercise at each load. On a separate visit, cardiac preload was increased via 7 ml·kg^{-1} intravenous Gelofusine infusion, and further augmented by a 45° passive leg-raise. Echocardiography was performed at rest, post-infusion and during the passive leg-raise. Brachial blood pressure was measured continuously via finger plethysmography, which was calibrated to manual blood pressure obtained at rest.

6.2.3 Transthoracic Cardiac Ultrasound Imaging: Resting Measures

All transthoracic echocardiography examinations were performed in accordance with **Chapter 3.** LV posterior wall thickness (PWT) and internal diameter (LVID$_d$) were measured from the 2D parasternal long-axis view at end diastole. Relative wall thickness (RWT) was calculated as 2 x PWT/LVID$_d$. LV mass was calculated according to the cube formula using 2D imaging (Lang *et al.*, 2015). LV length at end-diastole (LV length$_d$) was determined as the length from the mitral valve annulus to the apical subendocardium from the four-chamber view. LV sphericity index was calculated as LV length$_d$/diameter$_d$ from the apical 4 chamber view (Di Donato *et al.*, 2006). LV volumes were analysed using Simpson's biplane approach from the apical four chamber and two-chamber view by tracing the endocardial border at end-diastole and end-systole for LV EDV and LV ESV, respectively. SV was calculated by subtracting ESV from EDV and cardiac output was calculated as the product of heart rate and SV. Pulsed-wave Doppler recordings were obtained from an apical four-chamber view to assess trans-mitral early (E) and late (A) diastolic filling velocities, with the sample volume placed between the tips of the open valve.

6.2.4 Transthoracic Cardiac Ultrasound Imaging: Experimental Measures

LV SV was calculated using Simpson's biplane approach before and after Gelofusine infusion and during the passive leg-raise. Due to body position and nature of the strenuous activity during leg-press exercise, which compromised the ultrasound imaging window, it was not possible to collect apical two chamber images in most participants during the experimental pressure loading condition, due to inadequate image quality. Therefore, LV volumes were calculated using Simpson's monoplane approach from the apical four-chamber view throughout the leg-press intervention. Trans-mitral diastolic filling velocities

were obtained as described above for each stage of the experimental design. Speckle tracking derived strain values were obtained as detailed in **Chapter 3.6.4**.

6.2.5 Statistical analysis

All data were first assessed for normality using the Shapiro-Wilk test and visual inspection of Q-Q plots. One-way analysis of variance (ANOVA) was used to compare baseline measures between groups. The changes in hemodynamic and LV deformation measurements that occurred during either the pressure or volume loading conditions were expressed as percentage change of the mean values at baseline. Differences in the response between groups were compared using a two-factor repeated measures ANOVA (time*training status) with Sidak post-hoc analyses. Correlational analyses were used to explore potential relationships between the change in SV and global longitudinal strain characteristics from baseline to the final stage of each condition. LV mass and volumes were scaled to individual differences in body surface area (BSA), calculated using the (Du Bois & Du Bois, 1989) formula. Linear ratiometric scaling was achieved by simple division by BSA. Allometric scaling of LV mass was also performed to $BSA^{1.5}$ and LV volumes scaled to $BSA^{1.0}$, as previously recommended (Batterham *et al.*, 1999; Naylor *et al.*, 2008; Dewey *et al.*, 2008). For completeness, LV parameters were also scaled allometrically to BSA using the population *b* exponent. Scaling exponents for each measure were derived from the slope of the linear log-log plot of the independent variable (BSA) and the dependent variable (i.e., cardiac parameter of interest). In other words, LV dimensions were individually scaled to BSA raised to the power of the population (endurance, resistance and controls, combined) *b* exponent. The general allometric equation ($y = a \cdot x^b$) was used and linearised by taking the natural logarithms of both sides of the equation: $\log Y = \log a + b \log X$. exponent 'b' is simply the slope of the linear log-log plot, proportionality coefficient 'a' is calculated as the antilog of the Y-intercept term. All statistical analyses were performed using the Statistical Package for the Social Sciences version 24 (SPSS Inc.,

Illinois, United States of America). Alpha was set at $P < 0.05$ and data were expressed as mean ± standard deviation (SD). Effect sizes (Cohen's d) are reported to determine whether meaningful differences were present.

6.3 Results

6.3.1 Study Participants

Lifetime training years and training frequency were not different between the athletic groups (**Table 12**). $\dot{V}O_{2\,peak}$ was higher in those who were endurance-trained in comparison to non-athletic ($P < 0.001$) and resistance-trained males ($P < 0.001$). Additionally, 1RM was significantly greater in the resistance-trained group, compared to both endurance-trained ($P < 0.001$) and non-trained controls ($P < 0.001$). Heart rate was significantly greater in non-athletic controls in comparison with endurance-trained individuals ($P = 0.001$), however no significant differences were observed in resting systolic ($P = 0.791$) or diastolic blood pressures between groups ($P = 0.978$).

Table 12 Participant characteristics including demographic information and baseline haemodynamic measures.

	Control (*n* = 13)	Endurance (*n* = 15)	Resistance (*n* = 14)	One-way ANOVA *P* value
Demographics				
Age (years)	23 ± 3	29 ± 5*	24 ± 3†	**0.002**
Height (cm)	180 ± 9	180 ± 6	181 ± 6	0.870
Body Mass (kg)	75 ± 7	75 ± 6	87 ± 7*†	**< 0.001**
BMI (m^2)	23.8 ± 4	23.2 ± 1.7	26.8 ± 1.6*†	**< 0.001**
BSA (m^2)	1.94 ± 0.11	1.95 ± 0.11	2.08 ± 0.11*†	**0.004**
Body Fat %	15.5 ± 6.3	12.4 ± 4.8	12.5 ± 3.6	0.279
$\dot{V}O_{2\,peak}$ (ml·kg^{-1}·min^{-1})	40 ± 5	55 ± 9*	40 ± 4†	**< 0.001**
$\dot{V}O_{2\,peak}$ (ml·min^{-1})	2995 ± 244	4156 ± 498*	3467 ± 348*†	**< 0.001**
Leg-press 1RM (kg)	245 ± 62	275 ± 59	458 ± 38*†	**< 0.001**
Training History (years)		5 ± 2	6 ± 3	**0.543**
Training Freq. (session·wk)	1 ± 1	7 ± 2*	5 ± 1*	**< 0.001**
Hemodynamic				
SBP (mmHg)	124 ± 6	122 ± 8	123 ± 8	0.791
DBP (mmHg)	76 ± 7	75 ± 7	76 ± 7	0.978
Heart Rate (bpm)	58 ± 6	50 ± 6*	56 ± 8	**0.017**

BMI, body mass index; BSA, body surface area; 1RM, one-repetition maximum; SBP, systolic blood pressure; DBP diastolic blood pressure. *significant difference vs. control ($P < 0.05$), † significant difference vs. endurance ($P < 0.05$).

6.3.2 Left Ventricular Structure and Function at Rest

LV PWT ($P = 0.186$) and sphericity index ($P = 0.514$) were similar between groups (**Table 13**). In the endurance-trained group, LV mass scaled both ratiometrically ($P = 0.017$) and allometrically (BSA$^{1.5}$, $P = 0.025$; BSA$^{0.991}$, $P = 0.016$) was greater but RWT was significantly lower, in comparison to controls ($P = 0.024$), with no difference observed between resistance-trained and controls (LVmass/BSA, $P = 0.239$; LVmass/BSA$^{1.5}$, $P = 0.724$; LVmass/BSA$^{0.991}$, $P = 0.193$ and RWT, $P = 0.912$, respectively). Irrespective of scaling approach, SV was significantly greater in endurance-trained individuals compared to controls ($P = 0.007$). EDV was significantly greater in both endurance ($P < 0.001$) and resistance-trained ($P = 0.011$), in comparison to controls. However, when scaled to BSA, only endurance-trained had a greater EDV in comparison to controls (EDV/BSA, $P = 0.001$; EDV/BSA$^{1.0}$, $P = 0.008$; EDV/BSA$^{0.528}$, $P = 0.004$). Similarly, ESV was significantly greater in both endurance ($P < 0.001$) and resistance-trained ($P = 0.011$), compared to controls. When scaled to BSA, ESV was only greater in endurance-trained in comparison to controls ($P = 0.001$). LV longitudinal strain ($P = 0.716$), time-to-peak strain ($P = 0.582$), and time-to-peak strain rate ($P = 0.911$) were similar between groups at baseline. However, strain rate was significantly greater in controls in comparison to endurance-trained individuals at rest ($P = 0.048$).

Table 13. Left ventricular structure and function at baseline in athletes and non-athletic controls.

	Control (*n* = 13)	Endurance (*n* = 15)	Resistance (*n* = 14)	One-way ANOVA *P* value
LV Geometry				
LV end-diastolic length (cm)	9.2 ± 0.6	9.4 ± 0.6	9.6 ± 0.9	0.476
LV mass (g)	136 ± 17	156 ± 16*	158 ± 24*	**0.008**
LV mass/BSA (g/m^2)	70 ± 8	80 ± 8*	76 ± 11	**0.021**
LV mass/BSA (g/ m^2)$^{1.5}$	50 ± 6	57 ± 6*	53 ± 7	**0.026**
LV mass/BSA (g/ m^2)$^{0.911}$	74 ± 8	85 ± 8	81 ± 11	**0.018**
LV PWT (cm)	0.81 ± 0.05	0.80 ± 0.05	0.83 ± 0.05	0.186
LV RWT	0.33 ± 0.03	0.30 ± 0.02*	0.32 ± 0.03	**0.019**
Sphericity Index	1.77 ± 0.16	1.79 ± 0.10	1.74 ± 0.16	0.514
LV Function				
LV EDV (ml)	124 ± 12	155 ± 23*	146 ± 20*	**< 0.001**
LV ESV (ml)	48 ± 6	62 ± 11*	58 ± 9*	**< 0.001**
LV SV (ml)	76 ± 9	92 ± 15*	88 ± 14	**0.007**
LV EDV/BSA (ml/m^2)	64 ± 7	79 ± 11*	71 ± 10	**0.001**
LV ESV/BSA (ml/m^2)	25 ± 4	32 ± 5*	28 ± 5	**0.001**
LV SV/BSA (ml/m^2)	39 ± 5	47 ± 8*	42 ± 7	**0.009**
LV EDV/BSA (ml/m^2)$^{1.0}$	64 ± 7	78 ± 13*	70 ± 10	**0.010**
LV ESV/BSA (ml/m^2)$^{1.0}$	25 ± 4	31 ± 6*	28 ± 5	**0.011**
LV SV/BSA (ml/m^2)$^{1.0}$	39 ± 5	47 ± 8*	42 ± 7	**0.027**
LV EDV/BSA (ml/m^2)$^{0.528}$	88 ± 9	108 ± 17*	99 ± 14	**0.006**
LV ESV/BSA (ml/m^2)$^{0.493}$	35 ± 5	44 ± 8*	41 ± 6	**0.005**
LV SV/BSA (ml/m^2)$^{0.555}$	53 ± 6	63 ± 10*	58 ± 9	**0.022**
EF (%)	61 ± 4	60 ± 4	60 ± 4	0.651
E (cm·s^{-1})	0.90 ± 0.19	0.90 ± 0.15	0.80 ± 0.15	0.319
A (cm·s^{-1})	0.41 ± 0.08	0.38 ± 0.06	0.38 ± 0.08	0.803
E/A	2.28 ± 0.47	2.45 ± 0.48	2.12 ± 0.38	0.507
LV Longitudinal Strain Characteristics				
Strain (%)	-17.8 ± 2.4	-17.2 ± 1.0	-17.4 ± 2.3	0.716
Strain Rate (%·s^{-1})	-0.95 ± 0.16	-0.84 ± 0.07*	-0.86 ± 0.08	**0.048**
TTP Strain (%)	100 ± 5	100 ± 5	98 ± 4	0.582
TTP Strain Rate (%·s^{-1})	44 ± 11	47 ± 10	53 ± 10	0.911
Diastolic Strain (%)	1.61 ± 0.22	1.56 ± 0.21	1.43 ± 0.18	0.802
Diastolic Strain Rate (%·s^{-1})	119 ± 3	116 ± 2	119 ± 2	0.197

LV geometry measurements were obtained with the participant rested in the left lateral decubitus position. LV, left ventricle; PWT, posterior wall thickness; RWT, relative wall thickness; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; TTP, time-to-peak.
*significant difference vs. control (*P* < 0.05), † significant difference vs. endurance (*P* < 0.05).

6.3.3 Left Ventricular Response to Incremental Pressure Load

Heart rate and blood pressure increased to a similar extent during leg-press exercise across all three groups (**Table 14**). At lower intensities, no differences in SV were observed between groups (20% 1RM; $d = 0.68$, $P = 0.445$ and 40% 1RM; $d = 0.84$, $P = 0.190$). In contrast, the increase in cardiac output at 60% 1RM was significantly greater among resistance-trained individuals in comparison to controls ($92 \pm 15\%$ vs. $58 \pm 16\%$, $P < 0.001$). Furthermore, in line with the hypothesis for this study, when challenged with leg-press exercise at 60% 1RM, the resistance-trained group maintained SV closer to baseline values in comparison to the reduction in SV in controls (**Figure 24 A**; resistance-trained vs. controls, $d = 1.41$, $P = 0.004$). EDV was not different to baseline values and remained similar between groups at 20% 1RM ($d = 0.53$); however, at both 40% ($d = 0.96$) and 60% ($d = 1.33$), the reduction in EDV was markedly greater in controls in comparison to both athletic cohorts (**Figure 24 B**). In contrast, ESV appeared to increase in endurance-trained individuals while remaining relatively constant or decreasing minimally in resistance-trained and non-trained individuals (time*training status, $P = 0.086$). As a result, ESV was different between endurance-trained and controls at 40% 1RM ($d = 2.39$, $P = 0.038$) and 60% 1RM, though not meeting statistical convention for significance at the higher intensity ($d = 0.87$, $P = 0.088$; **Figure 24 C**). The pattern of change in trans-mitral Doppler measures E, A, and E/A across each stage was similar between groups (**Table 14**). Representative echocardiographic images are provided in **Appendix IV**: Supplementary Figure 9.
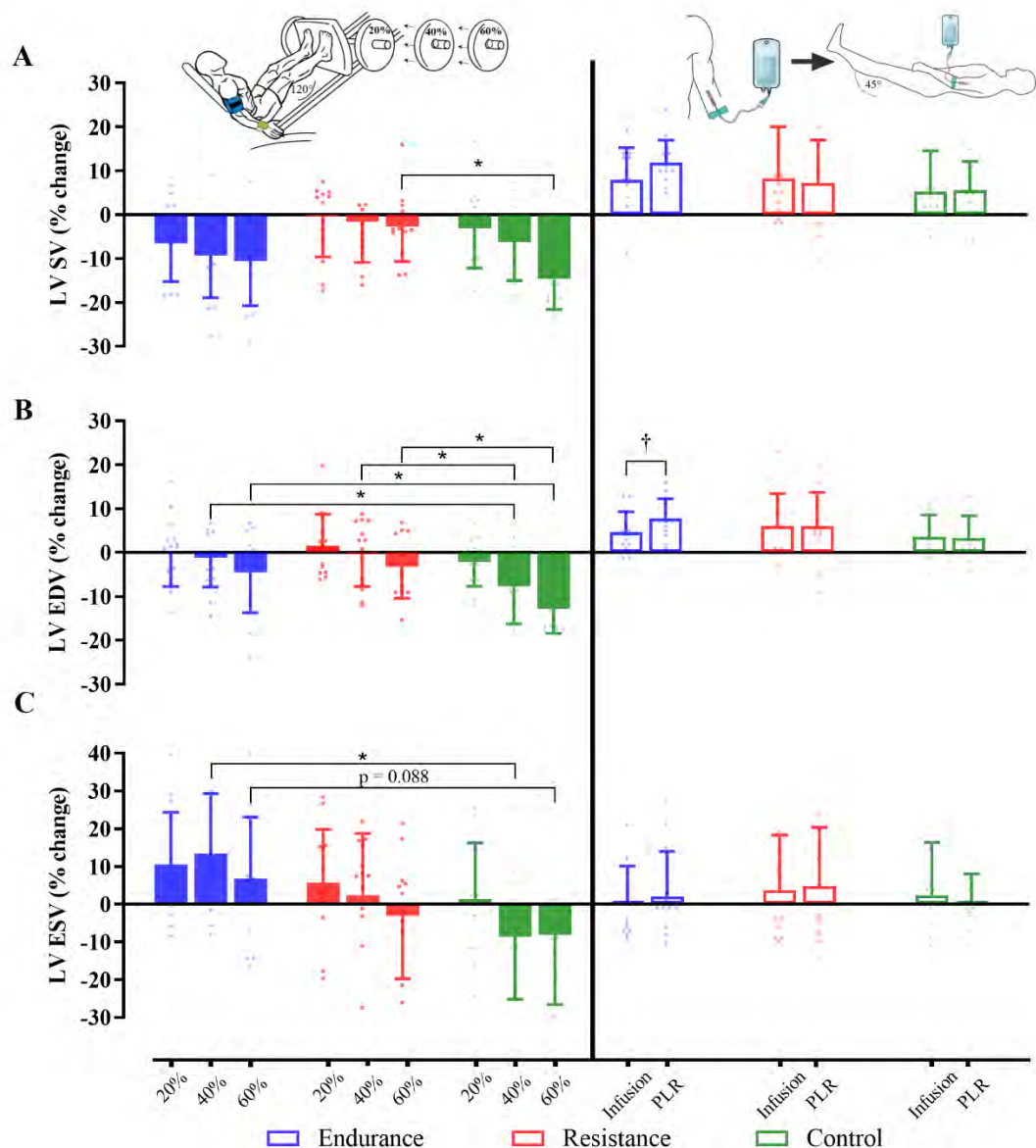
Figure 24. Hemodynamic left ventricular response following static double leg-press exercise at 20%, 40% and 60% of 1RM (left panels) and following 7 ml·kg^{-1} intravenous Gelofusine infusion and combined 45° passive leg-raise (PLR; right panels).

Endurance athletes (blue; $n = 15$ and $n = 13$ for leg-press and infusion condition, respectively), resistance athletes (red; $n = 14$ and $n = 13$, respectively) and non-athletic controls (green; $n = 13$ and $n = 11$, respectively). Data are displayed as percentage change from baseline. Panel *A* shows the change in stroke volume (SV), panel *B* shows end-diastolic volume (EDV) and panel *C* shows end-systolic volume (ESV) following both interventions. * significant difference vs. non-athletic controls at the same time-point ($P < 0.05$). ‡ significant difference within group between time-points ($P < 0.05$).

Table 14. Percentage change in hemodynamic variables from baseline in response to isometric leg-press exercise in non-athletic controls, endurance-trained and resistance-trained individuals.

	20% 1RM			40% 1RM			60% 1RM		
	Control	Endurance	Resistance	Control	Endurance	Resistance	Control	Endurance	Resistance
SBP (%)	17 ± 7	18 ± 7	17 ± 7	22 ± 8	24 ± 9	22 ± 7	22 ± 8	24 ± 10	26 ± 7
DBP (%)	16 ± 6	18 ± 9	20 ± 8	23 ± 6	26 ± 10	27 ± 9	25 ± 9	27 ± 12	31 ± 7
Heart Rate (%)	52 ± 17	69 ± 35	43 ± 19	77 ± 19	94 ± 39	70 ± 25	86 ± 19	107 ± 52	99 ± 23
Q (%)	47 ±19	57 ± 31	42 ± 24	67 ± 25	77 ± 42	67 ± 27	58 ± 16	86 ± 51	92 ± 15*
LV EDV (%)	-2 ± 6	0 ± 8	2 ± 7	-8 ± 9	-1 ± 7*	-0 ± 7*	-13 ± 6	-5 ± 9*	-3 ± 7*
LV ESV (%)	1 ± 15	11 ± 14	6 ± 14	-9 ± 17	13 ± 16*	2 ± 16	-8 ± 18	7 ± 16	-3 ± 17
LV SV (%)	-3 ± 9	-7 ± 9	0 ± 9	-6 ± 9	-9 ± 10	-2 ± 9	-15 ± 7	-11 ± 10	-3 ± 8*
E (%)	15 ± 13	10 ±16	9 ± 15	30 ± 23	18 ± 16	13 ± 16	39 ± 23	28 ± 22	22 ± 22
A (%)	85 ± 53	97 ± 63	81 ± 35	128 ± 65	140 ± 74	139 ± 83	179 ± 55	167 ± 86	194 ± 92
E/A (%)	-31 ± 17	-40 ± 19	-37 ± 14	-41 ± 21	-49 ± 15	-49 ± 12	-51 ± 7	-47 ± 18	-54 ± 11
Strain (%)	8 ± 18	4 ± 11	2 ± 9	12 ± 28	8 ± 17	8 ± 11	8 ± 19	11 ± 16	17 ± 15
Time-to-peak strain (%)	2 ± 8	7 ± 10	4 ± 8	9 ± 14	6 ± 11	4 ± 8	7 ± 8	12 ± 14	1 ± 6

1RM, one-repetition maximum; SBP, systolic blood pressure; DBP diastolic blood pressure; Q, cardiac output; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; E, peak early diastolic left ventricular filling velocity; A, peak late diastolic left ventricular filling velocity.

* significant difference vs. non-athletic controls at the same time-point ($P < 0.05$).

Secondary correlational analysis of longitudinal deformation characteristics during leg-press at 60% 1RM revealed a significant relationship between the change in SV and strain across all individuals (R = 0.537, *P* = 0.007; **Figure 25**). Subsequent between group analysis identified a significant delay in the time-to-peak strain in endurance-trained individuals in comparison to resistance-trained individuals (12 ± 14% vs. 1 ± 6%, respectively; *d* = 1.12, *P* = 0.021). As such, peak longitudinal strain was delayed until after the systolic period in endurance-trained individuals and occurred after 10% of the diastolic period had been completed (i.e., "*post-systolic shortening*", **Figure 26**). However, in non-athletic controls the 8 ± 8% increase in time-to-peak strain was not significantly different to either the endurance-trained (*P* = 0.522) or resistance-trained individuals (*P* = 0.364).
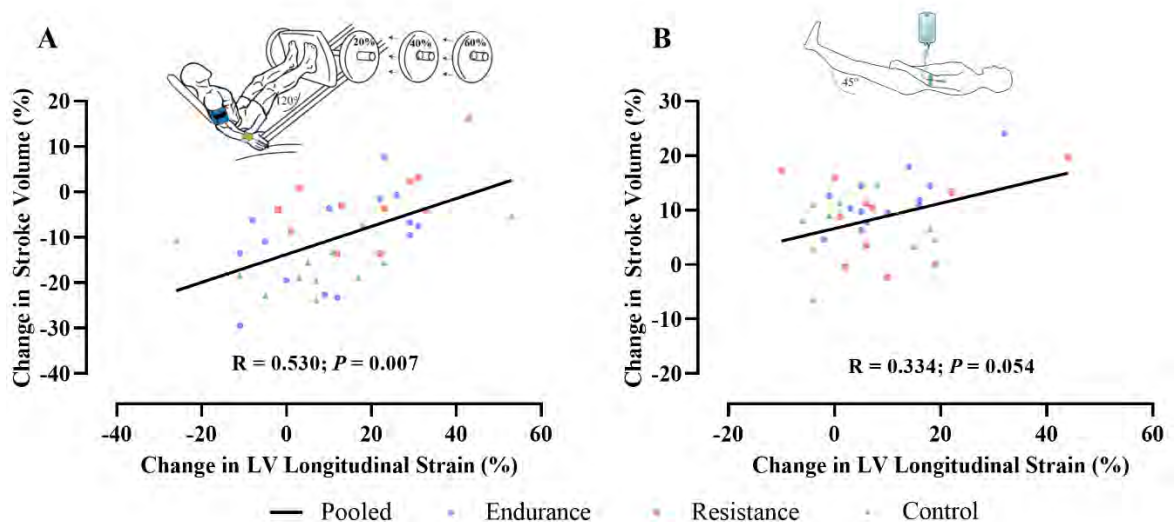
Figure 25. A. Grouped correlation analysis between the change in left ventricular (LV) stroke volume (%) and the change in LV longitudinal strain (%) during 60% 1RM leg-press exercise across all individuals (black line).

Individual data points represent endurance-trained individuals (blue circles; *n* = 15), resistance-trained individuals (red squares; *n* = 14) and non-athletic controls (green triangles; *n* = 13). *B*. Grouped correlation analysis between the change in LV stroke volume (%) and the change in LV longitudinal strain (%) following combined 7 ml·kg⁻¹ Gelofusine infusion and passive leg-raise across all individuals. Individual data represent endurance-trained individuals (*n* = 13), resistance-trained individuals (*n* = 13) and non-athletic controls (*n* = 11).
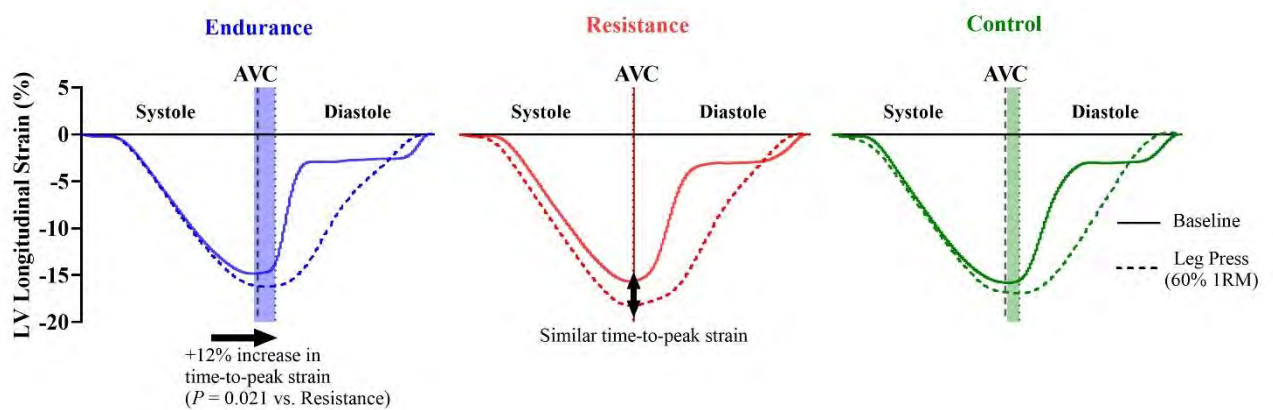
Figure 26. Temporal representation of left ventricular (LV) strain between groups at baseline (solid line) and during 60% 1RM leg-press exercise (corresponding dashed line)

Endurance-trained individuals (blue, $n = 15$), resistance-trained individuals (red, $n = 14$) and non-athletic controls (green, $n = 13$) and pooled data (black). Shaded area after aortic valve closure (AVC) represents post-systolic shortening following leg-press exercise as a % of the cardiac cycle.

6.3.4 Left Ventricular Response to Volume Loading

Gelofusine infusion (7 ml·kg^{-1}) was successfully completed in 13 endurance-trained (absolute infusion volume; 531 ± 47 ml), 13 resistance-trained (607 ± 51 ml) and 11 control participants (533 ± 58 ml). Participant noncompliance was due to needle phobia ($n = 1$, resistance-trained) and participant attrition ($n = 2$, control and $n = 2$, endurance-trained). Blood volume increased by a similar extent amongst all groups from pre- to post-infusion ($12 \pm 3\%$, $12 \pm 4\%$ and $13 \pm 4\%$; endurance, resistance, and control, respectively; $P = 0.867$) and blood pressure remained similar between groups throughout the experimental stages (**Table 14**). Differences in the heart rate response to volume expansion were noted between groups: no change was observed in endurance and resistance-trained individuals, whereas non-athletic controls experienced an increase of five beats per minute (**Figure 27**), though failing to reach conventional statistical significance ($d = 0.85$, $P = 0.061$).
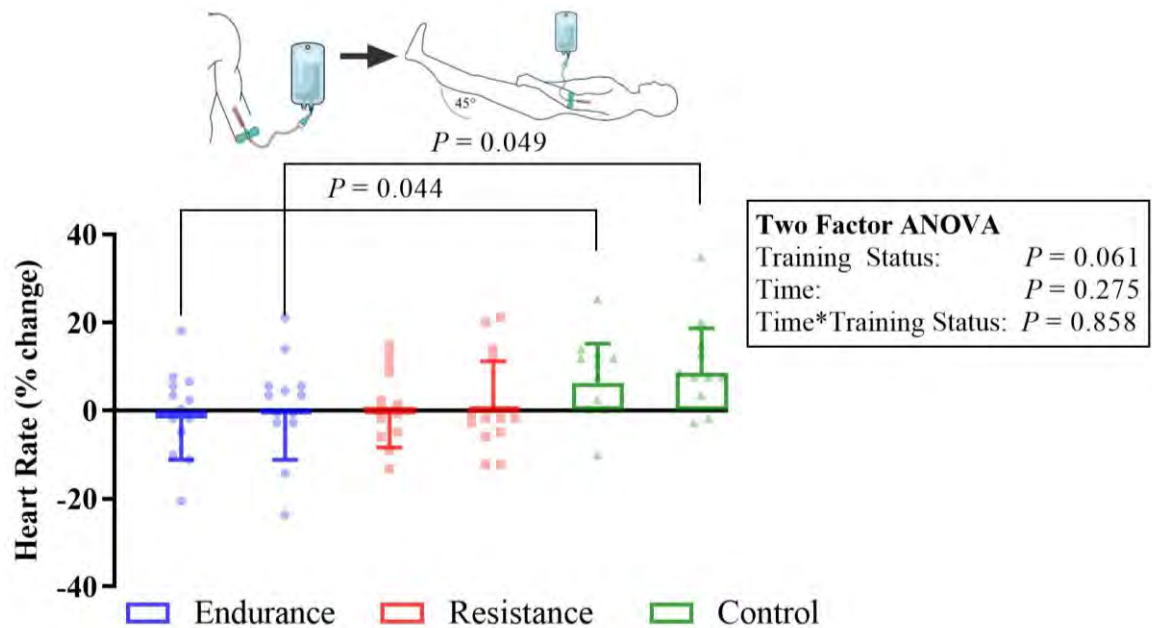
Figure 27. **Heart rate response (% change) following 7 ml·kg^{-1} Gelofusine infusion and subsequent passive leg-raise**

Endurance-trained individuals (blue circles; $n = 13$), resistance-trained individuals (red squares; $n = 13$) and healthy controls (green triangles; $n = 11$). Data are displayed as percentage change from baseline.

Contrary to the initial hypothesis, the mean increases in SV following plasma volume expansion were statistically similar between groups and remained comparable following the 45° passive leg-raise ($d = 0.93$, $P = 0.350$). However, unlike the resistance-trained and controls, endurance-trained individuals showed an additional increase in EDV following passive leg elevation after volume expansion ($5 \pm 5\%$ to $8 \pm 5\%$, $P = 0.018$; **Figure 24B**). ESV remained similar between groups following infusion and passive leg-raise ($d = 0.411$, $P = 0.618$). Despite differences in the heart rate response between groups, no significant differences in cardiac output, E, A or E/A were found between groups (**Table 14**). Though a positive relationship was found between the change in SV and longitudinal strain across all individuals ($R = 0.334$, $P = 0.054$; **Figure 25**), subsequent analysis of longitudinal strain characteristics revealed no between group differences. Representative echocardiographic images are provided in **Appendix IV**: **Supplementary Figure 10.**

Table 12. Percentage change in primary variables from baseline in response to 7 ml·kg⁻¹ intravenous Gelofusine infusion and subsequent passive leg-raise.

	Infusion			Passive Leg-Raise		
	Control	Endurance	Resistance	Control	Endurance	Resistance
SBP (%)	0 ± 6	-1 ± 4	-2 ± 5	-4 ± 12	3 ± 10	0 ± 7
DBP (%)	-3 ± 10	3 ± 8	-1 ± 9	1 ± 9	3 ± 5	2 ± 10
Heart rate (%)	6 ± 9	-2 ± 9	0 ± 8	9 ± 10	0 ± 11	0 ± 11
Q (%)	12 ± 15	7 ± 13	8 ± 14	15 ± 12	12 ± 14	8 ± 16
LV EDV (%)	4 ± 5	5 ± 5	6 ± 7	3 ± 5	8 ± 5‡	6 ± 8
LV ESV (%)	2 ± 14	0 ± 10	4 ± 14	0 ± 8	2 ± 12	5 ± 16
LV SV (%)	5 ± 9	8 ± 7	8 ± 12	5 ± 7	12 ± 5	7 ± 10
E (%)	12 ± 12	10 ± 26	15 ± 16	11 ± 11	18 ± 22	18 ± 23
A (%)	12 ± 12	7 ± 23	18 ± 34	15 ± 24	11 ± 21	18 ± 33
E/A (%)	4 ± 19	10 ± 32	1 ± 15	-2 ± 15	11 ± 21	-1 ± 20
LV Longitudinal Strain (%)	4 ± 7	9 ± 8	10 ± 13	4 ± 10	10 ± 9	10 ± 14
TTP Strain (%)	2 ± 4	1 ± 7	1 ± 5	1 ± 3	0 ± 5	2 ± 7

SBP, systolic blood pressure; DBP diastolic blood pressure; Q, cardiac output; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; E, peak early diastolic left ventricular filling velocity; A, peak late diastolic left ventricular filling velocity. ‡ significant difference within group between time-points ($P < 0.05$).

6.4 Discussion

The primary findings of this study are that: i) during high-intensity isometric leg-press exercise, SV is well maintained in resistance-trained males only (**Figure 24 A**), which may be a consequence of preserved timing of peak LV longitudinal myocardial deformation (**Figure 26**); ii) following an acute plasma volume expansion, the increase in EDV and SV are similar between endurance-trained, resistance-trained and controls, however, iii) further augmentation of EDV via passive leg-raise was only observed in the endurance-trained group (**Figure 24 B**). To my knowledge, this is the first study to examine the LV functional response to both isometric resistance exercise and increasing circulating blood volume in the same group of individuals. Together, these data support the potential of training-specific functional remodelling of the LV to different stimuli, even in the absence of marked

structural adaptations. Furthermore, this data highlights the potential physiological trade-off that may accompany training-specific LV adaptation, whereby the ability to functionally respond to either a volume or pressure load may be at the detriment of managing the alternate stimulus.

6.4.1 Adaptation in the Left Ventricular Functional Response to Isometric Leg-Press Exercise

In the present study, as has been shown previously (Urhausen & Kindermann, 1999; Spence *et al.*, 2011; Oxborough *et al.*, 2019), well-trained but non-elite resistance-trained individuals did not possess the concentric LV remodelling pattern previously suggested (Morganroth *et al.*, 1975; Pluim *et al.*, 2000; D'Andrea *et al.*, 2002; Baggish *et al.*, 2008*a*; Mihl *et al.*, 2008). Despite this, the resistance-trained group were better able to maintain SV at near baseline values across each incremental stage of isometric exercise, even with similar increases in blood pressure across all groups. In contrast, at 60% 1RM the endurance-trained group and non-athletic controls experienced a decrement in SV of ~11% and ~15% respectively.

The mechanisms underlying the divergent LV volumetric response to resistance exercise remain speculative, but may involve changes in specific cellular and molecular adaptation of the myocardium and extracellular matrix (Melo *et al.*, 2018; Domańska-Senderowska *et al.*, 2019). Cardiomyocyte contractility may increase following resistance training via myosin ATPase activity and enhanced calcium influx, as has been shown in rodent studies (de Cássia Cypriano Ervati Pinter *et al.*, 2008; Fernandes *et al.*, 2015). In turn, these adaptations would increase the force of contraction, thereby improving the myocardial capacity to maintain efficient ejection in the face of an increased afterload. Secondary analysis of LV longitudinal deformation supports this argument, showing that those with the greatest increase in myocardial deformation during heavy resistance exercise

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were better able to maintain SV (**Figure 25A**). In contrast, cardiac adaptation with endurance-training may have had a detrimental influence on the LV response to isometric exercise. The increase in time-to-peak strain in the endurance cohort is suggestive of a compromised systolic functional response, with a substantial portion of shortening occurring after aortic valve closure, which therefore does not contribute to the ejection of blood and impedes early diastolic relaxation. This pattern of post-systolic shortening of the LV is similar to that previously observed in systemic hypertension (Nogi *et al.*, 2016) and in the RV of healthy populations during an acute increase in pulmonary artery pressure (Stembridge *et al.*, 2014; Dedobbeleer *et al.*, 2015; Naeije & Badagliacca, 2017). Additionally, whilst the more compliant chamber of an endurance athlete is beneficial when venous return increases (Levine *et al.*, 1991), greater chamber compliance may cause a disproportionately larger decrease in SV when venous return is reduced, for example during some forms of isometric exercise (Alegret *et al.*, 2015). The heterogeneous EDV response and relative maintenance of SV in resistance-trained individuals may also be related to differential cardiopulmonary interactions between the groups. Abdominal pressure, intrathoracic pressure, right atrial pressure, and lung volumes are likely to have increased during leg-press exercise, thereby reducing venous return (Alegret *et al.*, 2015; Cheyne *et al.*, 2018). Indeed, the decrease in SV in controls was accompanied by a reduction in EDV, suggestive of an underfilling of the LV, which differs mechanistically to endurance athletes, in whom a decrease in SV appears to be driven by an increase in ESV. This elevation in ESV may reflect a compromised ability to maintain systolic performance during an acute afterload challenge, reflected by a significant increase in post-systolic shortening. The additional residual volume in the ventricle after ejection, combined with venous return, likely moderates the reduction in EDV in the endurance-trained group, in comparison to controls. As recently proposed by Shave et al. (2019), it is possible that the divergent hemodynamic stimuli brought about by chronic endurance and resistance training leads to

differential cardiac adaptations, which compromise the heart's ability to accommodate the alternate volume or pressure challenge. The data from this study further support this contention, highlighting a potential physiological trade-off in the endurance athlete's capacity to cope with increasing systolic pressure. Other multimodality, mechanistic investigation in rat hearts, has shown that while resting LV functional measures are relatively unchanged by intense lifetime exercise, due to the disproportionate increase in RV wall stress during intense exercise (La Gerche *et al.*, 2011), the RV may be more susceptible to detrimental remodelling at the extremes of exercise load (Sanz-de la Garza *et al.*, 2017*b*). Further research is warranted to examine both the mechanisms responsible for the seemingly divergent functional LV remodelling in athletes of different sports, as well as the potential functional RV remodelling in response to hemodynamic perturbation.

Whether resistance-trained athletes also demonstrate preserved LV twist mechanics in response to a transient afterload increase is yet to be answered. An acute increase in afterload has been shown to decrease LV torsion in animal studies (Kroeker *et al.*, 1995; Dong *et al.*, 1999) and in reportedly healthy (but not specifically athletic) individuals during isometric hand grip exercise (Weiner *et al.*, 2012) and double leg press exercise (Stohr *et al.*, 2017). However, brief isometric knee extension exercise did not impair twist mechanics, which the authors put down to a relatively mild increase in blood pressure (Beaumont *et al.*, 2017*b*). As such, the type of resistance exercise performed can have a heterogeneous effect on LV afterload, LV mechanics, and LV volumes. Further work is required to compare LV mechanics in resistance athletes vs non-athletic controls immediately after resistance exercise (wherein a recovery of SV and supercompensation of untwisting rate has been observed exercise (Stohr *et al.*, 2017)), and in response to multiple repetitions and sets, as is common with resistance type training. Relative preservation of systolic (and diastolic) mechanics in resistance athletes, as demonstrated in the present

findings, may promote earlier recovery or preservation of stroke volume and LV contractility.

6.4.2 Adaptation in the Left Ventricular Functional Response to an Increased Circulating Blood Volume

Previous studies using lower body negative pressure and saline infusion to manipulate cardiac preload have shown that for any given LV filling pressure, endurance athletes have a greater EDV (Levine *et al.*, 1991). The findings from this seminal study indicates that endurance athletes have greater LV chamber compliance in comparison to sedentary controls. Consistent with these findings, endurance-trained individuals, unlike resistance-trained individuals and healthy controls, were capable of further EDV augmentation (through passive leg elevation) even when already volume-expanded. Within the methodological confines of the present study, it is difficult to ascertain the acute limitation to ventricular filling between groups, though it likely reflects a dependency upon both the compliance characteristics of the myocardium and pericardial constraint (Kroeker *et al.*, 2003). It is possible that the "tightness" of the pericardium ultimately limits ventricular filling and that pericardial remodelling (Esch *et al.*, 2007), subsequent to the repetitive increases in circulating blood volume associated with prolonged-training, may explain the ability for endurance-trained individuals to "accept" a greater EDV.

Interestingly, whilst cardiac output increased across all groups following volume loading, this was achieved via increased SV in athletic populations compared to an augmentation of heart rate with preserved SV in controls (**Figure 27**). Following 30 ml·kg^{-1} saline infusion, (Levine *et al.*, 1991) also observed a significant elevation in heart rate in non-athletes, by 12 bpm ($P < 0.01$), but not in endurance athletes (7 bpm, $P > 0.05$). This chronotropic sensitivity in untrained individuals may be due to mechanical factors, such as reduced cardiac chamber compliance (Levine *et al.*, 1991; Bhella *et al.*, 2014) and

peripheral vascular distensibility (Rakobowchuk *et al.*, 2008; Ashor *et al.*, 2014), or perhaps due to intrinsic pressure receptor reflexes (Bainbridge, 1915; Moore *et al.*, 2004). It is unlikely, however, that this is a response of a single autonomic reflex, but rather a reflection of the complex relationship between baseline autonomic tone (Danson & Paterson, 2003), sinoatrial remodelling (D'Souza *et al.*, 2014), pressure receptor reflexes (Hainsworth, 1991) and/or altered stretch receptor sensitivity (Goetz, 1965).

6.4.3 Clinical Implications

Previous studies examining the influence of exercise training in both non-clinical and clinical populations have focused largely on markers of structural or resting functional remodelling. Many of these studies have shown little or modest adaptations to training (Dubach et al., 1997; Myers et al., 2002). These results suggest the potential for positive functional remodelling, even in the absence of marked changes in structure. Accordingly, even though exercise-training interventions may not result in gross changes in myocardial architecture, it is possible that functional adaptation as evidenced in participants in the current study, may reduce overall myocardial stress and could be clinically relevant in patient populations. Potential clinical implications, however, remain speculative and subject to further investigation. Furthermore, to my knowledge, this is the first study to non-invasive experimentally induce LV post-systolic shortening, which may have clinical utility. For example, post-systolic shortening during temporary coronary occlusion predicts functional recovery after reperfusion (Hosokawa et al., 2000). Therefore, substitution of coronary occlusion with isometric exercise to elicit post-systolic shortening may represent a non-invasive alternative. Future work should examine timing of shortening during isometric hand-grip exercise, which would represent a more accessible stimulus for clinical utilisation, and enable easier access to imaging windows for the sonographer.

6.4.4 Study Limitations

There are several limitations that must be acknowledged. First, the small sample size is a significant limitation; however, this is the first study to compare the LV response to incremental pressure and volume perturbations in the same group of differentially trained individuals. Further investigation of sport-specific functional LV remodelling is warranted in a larger cohort, and should also consider responses in individuals with substantial cardiac remodelling. A detailed history of training intensity was not captured, and therefore the influence of overall training load cannot be discerned. Additionally, it should be acknowledged that the endurance-trained cohort was older than those resistance-trained, however controlling for age as a covariate did not alter the findings of this study. Isometric exercise was performed without a Valsalva manoeuvre to facilitate data collection; however this exercise is unlikely to perfectly reflect the typical training conditions of resistance athletes. Furthermore, from these data and others (Lentini *et al.*, 1993; Haykowsky *et al.*, 2001; Alegret *et al.*, 2015), it is evident that certain forms of resistance exercise, including heavy leg-press, can cause LV underfilling. As such, different forms of resistance exercise may influence preload as well as afterload, which may be relevant for physiologic adaptation. Despite asking participants to refrain from engaging the Valsalva manoeuvre, it is likely that intrathoracic pressure was altered during the leg press protocol, as some degree of trunk stabilisation is mandatory during heavy resistance exercise. Haykowsky et al. (2001) eloquently demonstrate (in a small population of five resistance trained men) the potentially mitigating influence of increasing intrathoracic pressure on LV wall stress specifically during a brief Valsalva manoeuvre. However, comprehensive investigation of the fluctuations intrathoracic pressure, internal chamber pressure, and left, and right ventricular wall stress throughout prolonged or repetitive resistance exercise remain an important area of research that has received little scientific attention. In the present study, it is difficult to ascertain the mechanisms which underpin the preserved LV filling in

resistance-trained individuals, and whether this is due to a difference in cardiopulmonary interaction and subsequent modulation of LV filling, or enhanced LV deformation. Additionally, data reported are only relevant for young healthy men. Specific studies to examine the female athlete's heart which are adequately powered to explore sex differences are warranted and are currently being undertaken (Howden *et al.*, 2015; Williams *et al.*, 2017; Kooreman *et al.*, 2019).

6.5 Conclusion

This study provides novel data that supports the potential of stimulus-specific functional remodelling of the LV, even in the absence of marked structural adaptations. In response to a marked hemodynamic pressure load, resistance-trained individuals better maintained SV, which was coupled with preserved longitudinal deformation characteristics. Conversely, in a volume-loaded state, only endurance athletes were capable of further increasing EDV. Further research is warranted to examine the mechanisms which underpin these training-specific differential responses.

6.6 Study Hypotheses

Null Hypothesis: The LV functional response to a change in haemodynamic load would not be different between resistance-trained, endurance-trained individuals or nonathletic controls (REJECT).

Alternate Hypothesis: Athletic training would be associated with training-specific adaptation in the LV functional response to a change in haemodynamic load (ACCEPT).

Supplemental Materials: Appendix IV

Supplementary Figures 9 – 10

Chapter 7

General Discussion

Chapter 7. General Discussion

7.1 Summary

The over-arching aim of this thesis was to examine functional remodelling of the athlete's heart, and to distinguish specific adaptation of resistance-trained from endurance-trained individuals. Accordingly, this thesis i) assessed normal RV function in endurance athletes at rest, with specific examination of region-specific adaptation, ii) investigated the functional RV response to haemodynamic 'volume' loading in endurance athletes, and iii) assessed the functional LV response to haemodynamic 'volume' and 'pressure' loading in both endurance and resistance-athletes. This chapter summarises the main findings of the thesis and discusses the clinical significance of the findings before recommendations for future directions are made and limitations acknowledged.

7.2 Summary of Key Findings

In line with the aims set out in **Chapter 2.9**, the key findings are outlined in **Figure 28**. The first main finding from this thesis was that, in addition to structural remodelling, endurance training is associated with an elevated RV systolic pressure at rest, which is further increased (in comparison to non-athletes) during exercise. Furthermore, in agreement with the hypotheses, functional adaptation of the athlete's RV is characterised by a region-specific remodelling, which manifests as an elevated base-to-apex longitudinal strain gradient, due to a lower longitudinal strain at the base, and greater strain at the apex, in comparison to controls.

This thesis also examined the ventricular *functional response* to specific haemodynamic perturbation. In agreement with Shave et al. (2019), stimulus-specific LV functional remodelling was also demonstrated. The original findings of Shave et al. (2019) were extended, by first demonstrating that functional remodelling in athletes is not dependent on overt structural remodelling. Furthermore, previous work assessing the

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ventricular response to specific haemodynamic perturbation are limited by utilisation of small muscle group exercise, and rely on SV data only, without consideration of ventricular volumes and deformation (Wasfy *et al.*, 2019; Shave *et al.*, 2019). In response to an isometric leg-press exercise designed to increase LV afterload, resistance athletes better maintained SV in comparison to non-athletic controls that was supported by preserved LV ESV and time-to-peak longitudinal shortening. Conversely, in a volume loaded state, only endurance athletes were capable of further increasing LV EDV, despite a similar increase in RV area. Nonetheless, longitudinal strain at the base of the RV increased by a greater magnitude than controls in response to an increase in circulating volume. As such, it is proposed that the cardiac phenotype associated with exercise training is not simply characterised by differences in resting structure and function, but also by a functional response to changes in haemodynamic load.
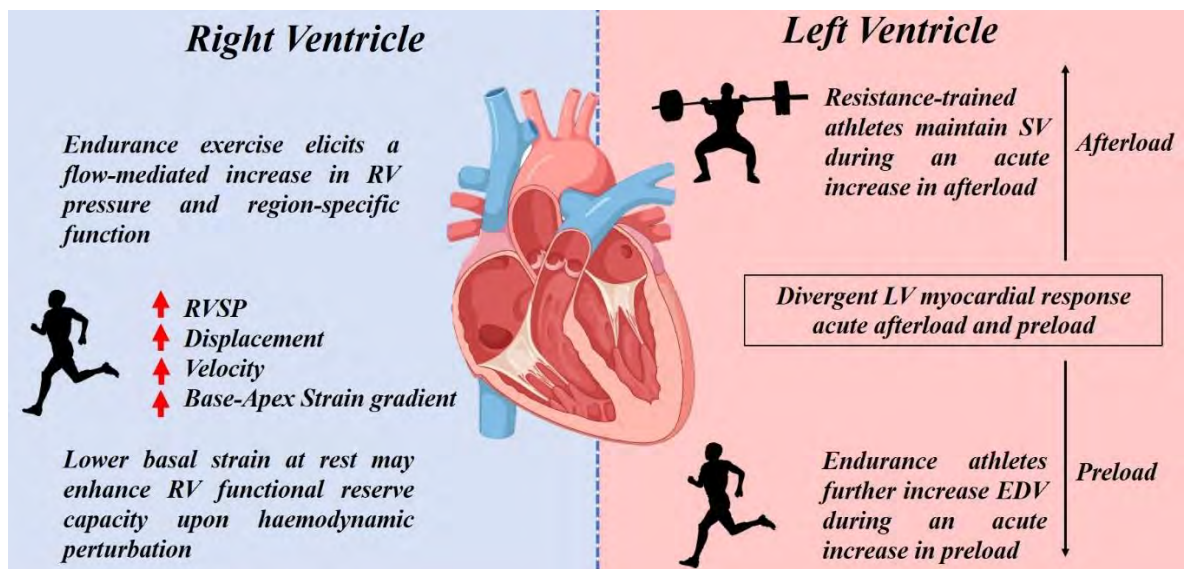
Figure 28. Schematic summarising the key findings of this thesis.

Arrows in boxes depict significant differences in comparison to non-athletic controls. RVSP, right ventricular systolic pressure.

7.3 Functional Remodelling of the Athlete's Heart; Functional Remodelling at Rest

Functional remodelling of the endurance athlete's LV is well established, as discussed in **Chapter 2**. Enhanced diastolic function has been extensively evidenced (Pluim *et al.*, 2000; Utomi *et al.*, 2013; Beaumont *et al.*, 2017*a*). Systolic function, however, may be depressed in these athletes (Galderisi *et al.*, 2015; Beaumont *et al.*, 2017*a*), since an eccentrically remodelled ventricle requires a lower magnitude of contraction to maintain normal SV, at rest. In contrast to the extensive literature studying LV function, there has been a paucity of study into the normal RV function in athletes. However, the increased availability of commercially available imaging techniques, such as echocardiography, combined with sufficient technological advancements to appropriately image the geometrically complex RV, has allowed an expansion of investigation in this area within the last decade. As such, **Chapter 4** sought to quantitatively summarise normal RV systolic function in endurance athletes, with specific comparison with non-athletic counterparts. Long-term endurance training was associated with an enhanced RV systolic function, as assessed by conventional indices (tricuspid annular displacement and velocity). Yet, consistent with structural RV remodelling (Oxborough *et al.*, 2012*b*; Prior & La Gerche, 2012; D'Andrea *et al.*, 2013; Bohm *et al.*, 2016; D'Ascenzi *et al.*, 2017*a*), myocardial functional adaptation is region-specific in comparison with non-athletic controls, longitudinal deformation at the base of the RV was lower in endurance athletes at rest, whereas apical deformation was greater, possibly as a compensatory adaptation or altered myofiber orientation (Hill *et al.*, 2014). This region-specific adaptation observed in **Chapter 4** was not corroborated in experimental **Chapter 5**, whereby regional strain at rest was similar between athletes and non-athletic controls. However, this disparity may be due a threshold of training volume (intensity and duration) required to evoke discrete myocardial adaptation (Sanz-de la Garza *et al.*, 2017*b*). Furthermore, similar to most studies included in **Chapter 4**, the small sample size was likely underpowered to detect subtle differences in RV function in athletes and

non-athletes. The comprehensive meta-analysis in **Chapter 4**, which was sufficiently powered, therefore reveals normal changes in RV function which may be expected in endurance athletes.

It could be speculated that altered loading conditions associated with increased blood volume in athletes may alter function, and may disproportionately influence different regions of the RV due to heterogeneous wall stress distributions (Gold *et al.*, 2019). Interestingly, the same pattern of regional RV function demonstrated in **Chapter 4** (i.e., lower basal strain and greater apical strain) is also displayed in some individuals with RV volume overload due to atrial septal defect (Van De Bruaene *et al.*, 2011; Dragulescu *et al.*, 2013). However, the mechanisms underpinning the region-specific functional adaptations observed in athletes in **Chapter 4** remain poorly understood. Repetitive exposure to elevated haemodynamic load may elicit changes in cellular and extracellular fibre alignment; in rats subjected to chronic pressure overload, for example, both myocardial and collagen fibres were re-aligned to a more longitudinal orientation (Hill *et al.*, 2014). Since contractile force occurs along the preferred fibre direction in the RV free wall (Armour *et al.*, 1970), region-specific alterations in RV free-wall strain may indeed reflect regional alterations in myocardial and extracellular fibre alignment. As a further complication, the relative presence of biological factors acting as mechano-transducers may also influence the type and extent of remodelling (Friedberg *et al.*, 2013; Nielsen *et al.*, 2017), which is supported by the disparate location of fibrosis in relation to areas of high wall stress in animal models of pulmonary artery banding (Gold *et al.*, 2019).

Exercise adaptation is also associated with changes in the autonomic nervous system, with higher parasympathetic tone (Fu & Levine, 2013). Since the RV is densely innervated by autonomic fibres (Hasan, 2013), altered neural regulation may influence ventricular function. In support of this, vagal stimulation prolongs normal base-apex-

infundibulum sequence of RV contraction (Dell'Italia, 1991). Altered adrenergic receptor sensitivity and distribution has also been speculated as a mechanism responsible for altered regional right ventricular function in pathological overload conditions (Shah *et al.*, 2000; Brodde *et al.*, 2001; Van De Bruaene *et al.*, 2011), however this is unlikely to play a role in exercise-induced functional remodelling, since functional reserve is maintained in response to exercise (La Gerche *et al.*, 2012*a*; Claeys *et al.*, 2020). Concomitant remodelling of the LV may also be responsible for the altered RV function observed in athletes, since a significant proportion of RV systolic pressure and ejection of blood is a direct result of left ventricular contraction (Santamore & Dell'Italia, 1998). Moreover, superficial RV myofibres become more oblique towards the apex, eventually spiralling to form the deep myofibres and superficial fibres of the LV (Nielsen *et al.*, 2009; Sanz *et al.*, 2019). As such, it is possible that deformation of the apical segment may be directly influenced by changes in the LV, although this remains speculative.

It is also plausible that the findings of lower regional strain and strain rate at the base may reflect subclinical myocardial damage from cumulative exercise, that could manifest as a potential substrate for arrythmia (La Gerche & Heidbuchel, 2014). Indeed, acute RV dysfunction in humans following prolonged exercise has been evidenced by a comprehensive meta-analysis (Elliott & La Gerche, 2015). Furthermore, animal studies have highlighted signs of fibrosis in conjunction with a segment-specific reduction in function at the RV base, and reduced RV contractility at rest (Benito *et al.*, 2011; Sanz-de la Garza *et al.*, 2017*b*). However, maladaptive remodelling is unlikely in the young athlete participants used throughout this thesis. Alternatively, similar to that which has been proposed for altered function in the LV (Nottin *et al.*, 2008), lower myocardial deformation at the base of the RV may reflect an enhanced reserve capacity, to be utilized during states of increased haemodynamic load. In **Chapter 5**, the increase in basal longitudinal deformation in response to an expanded central blood volume was greater in endurance-

trained individuals, in comparison with non-athletic controls. Additionally, the few studies that have assessed RV wall mechanics during exercise have demonstrated normal RV contractile reserve in athletes (La Gerche *et al.*, 2012*a*; Sanz-de la Garza *et al.*, 2017*a*; Claeys *et al.*, 2020). This finding supports the hypothesis that exercise-induced RV remodelling involves a region-specific adaptation in the RV functional response during an increase in preload.

7.4 Exercise-Induced Functional Remodelling; Response to Haemodynamic Perturbation

7.4.1 The Influence of an Acute Increase in Preload on Left Ventricular and Right Ventricular Function and Interaction in Athletes

In agreement with previous literature (Levine *et al.*, 1991), the present thesis demonstrates that endurance athletes have an increased LV diastolic reserve, reflected by an increased capacity to augment LV EDV when challenged with an increase in circulating volume. The adaptations resulting in this functional response are likely to be mediated by the repetitive exposure to high filling pressures during intense exercise at high cardiac outputs (Matsuda *et al.*, 1983; Mihl *et al.*, 2008; Périard *et al.*, 2016). As such, it may be speculated that remodelling of the endurance-trained LV favours an increased capacity to accommodate volume, presumably to meet the intense volume demands of endurance exercise.

Interestingly, whilst only endurance-trained individuals were capable of further increasing LV EDV with subsequent passive leg raise, RV cavity area increased by a similar extent in endurance, resistance and non-athletic controls (**Figure 29 A, left)**. Since the chambers of the heart are surrounded by the pericardium, which may constrain enlargement of cardiac chambers, it is possible that, in controls and resistance-athletes, the external constraint on the LV increased concomitant to the increase in RV cavity area. In contrast, the external constraint may have been less in endurance-trained individuals, resulting in an

increased capacity to further increase LV EDV when RV area is increased, as visually depicted in **Figure 29 B**. Similar findings have been observed by others using lower body positive pressure to influence haemodynamic loading conditions (Esch *et al.*, 2007). An increase in RV end-diastolic size could restrict LV filling (i.e., diastolic ventricular interaction) by increasing pericardial pressure and/or by shifting the septum towards the LV, due to a decreased interventricular septal pressure gradient, thereby temporarily decreasing LV compliance (Mitchell *et al.*, 2005). However, since eccentricity index was not significantly different between groups in this study (**Figure 29 B**), altered direct ventricular interaction is unlikely to explain observed differences between endurance athletes and resistance-trained and non-athletic counterparts. Furthermore, pericardial constraint and/or remodelling following endurance training remains a contentious topic requiring further investigation. Further, in contrast to speculation of pericardial remodelling in athletes, it may be argued that endurance training may increase external constraint due to an enlarged heart confined within the intrathoracic space (Stickland *et al.*, 2006*b*; La Gerche *et al.*, 2017).
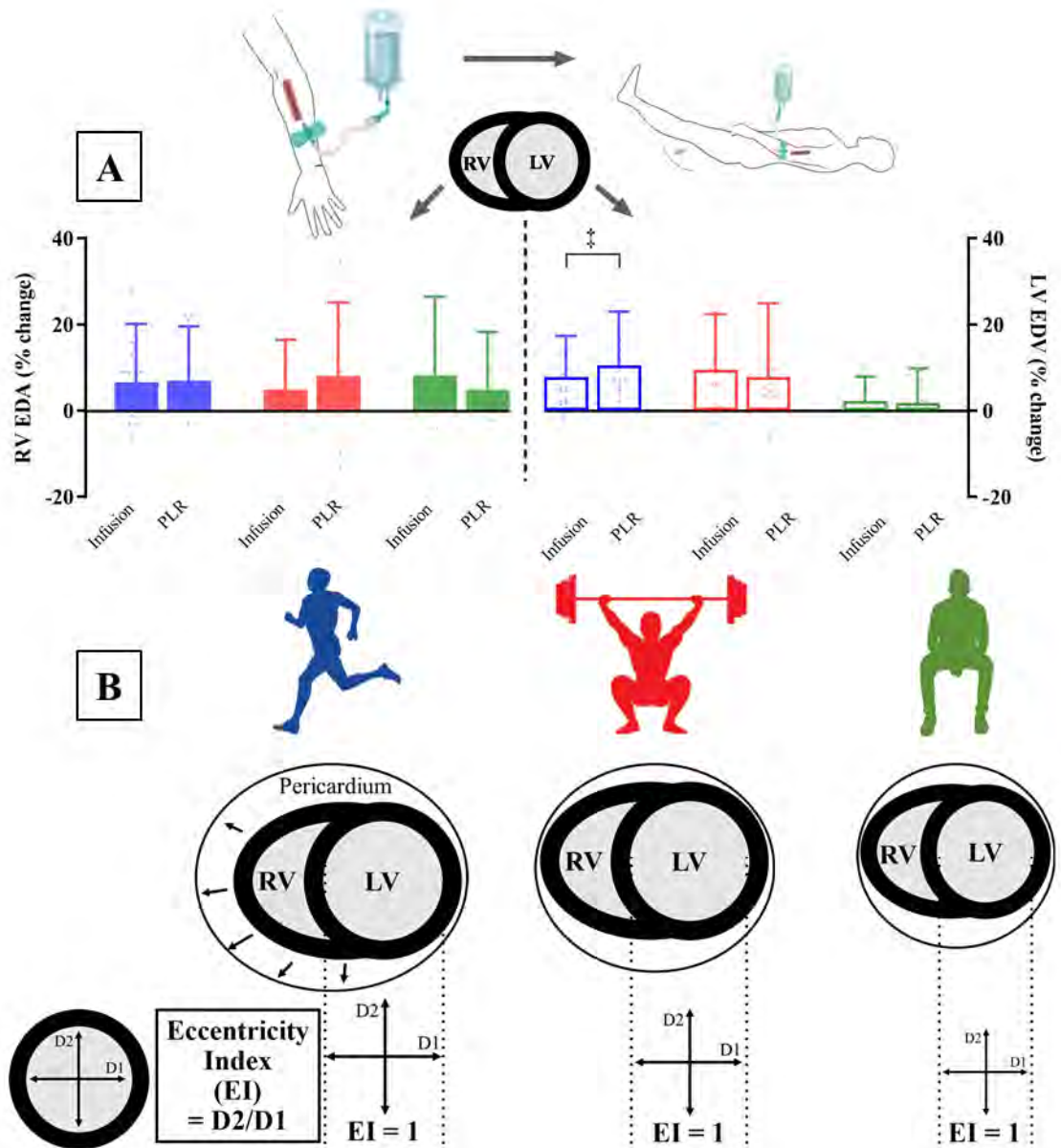
Figure 29. Right ventricular end-diastolic area (RV EDA) response (left), and left ventricular end-diastolic volume (LV EDV) response (right) to 7 ml/kg intravenous Gelofusine infusion and combined 45° passive leg raise (PLR).

Endurance athletes (blue) resistance athletes (red) and non-athletic controls (green). Black circle around LV and RV represents the pericardium. Values are presented as percentage change from baseline. ‡ significant difference within group between time-points ($P < 0.05$).

7.4.2. Divergent Left Ventricular Myocardial Response to an Acute Afterload Challenge in Resistance vs. Endurance Athletes

In **Chapter 6**, it was demonstrated that resistance-trained individuals were better able to maintain SV (-3%) during a marked haemodynamic pressure stimulus, in comparison to endurance-trained individuals (-11%). Similar findings have been demonstrated recently in American football players during isometric hand grip exercise; however the preserved SV in these individuals appeared to be related to the comparatively thicker LV wall (Shave *et al.*, 2019). The concentric remodelling in this context may mitigate increasing wall stress during a pressure surge and facilitate ventricular-arterial coupling via preserved systolic function. However, findings from **Chapter 6** demonstrate that SV is maintained in resistance athletes during a brief pressure challenge, despite an absence of overt structural remodelling and wall thickening. As such, it may be postulated that LV remodelling following resistance training is not dependent on myocardial hypertrophy, *per se*, but may involve cellular and molecular adaptation of the myocardium that enhance calcium handling. In this regard, the enhanced capacity for resistance athletes to maintain SV during a brief pressure surge may be due to cellular adaptations related to the Anrep effect (autoregulatory method in which myocardial contractility increases with afterload, instigated by repetitive, intermittent exposure to increasing afterload during stimulus specific exercise training). The Anrep effect has recently been demonstrated in humans during hand-grip exercise, which evoked an increase in contractility (end-systolic elastance) as measured by pressure-volume loops (Reil *et al.*, 2020). Currently, there are no studies that have assessed the potential training effect on the Anrep effect, although mechanisms which diminish or abolish the Anrep effect have been neatly summarised (Cingolani *et al.*, 2013). Nonetheless, angiotensin II appears to play an integral role in the initiation of the Anrep effect. Polymorphisms of the angiotensin converting enzyme, resulting in altered angiotensin II levels and which appear to partly dictate athletic success

to power sports (ACE D allele (Pescatello *et al.*, 2006; Ahmetov & Fedotovskaya, 2015; Peplonska *et al.*, 2017), may also contribute to an adequate Anrep effect. Angiotensin II represents just one step of a complex series of pathways that may contribute to these findings. Future study is required to corroborate the findings of this thesis, which suggest an enhanced myocardial response to an increase in afterload, in resistance-trained athletes. Determination of wall stress during different phases of resistance exercise in both resistance-trained and untrained counterparts, with specific consideration of changes in intrathoracic pressure would also contribute to our understanding of the acute consequence of resistance exercise.

In contrast to the enhanced functional response of resistance athletes, LV ESV was elevated among endurance-trained individuals during the pressure stimulus, suggesting a reduced ability to contract in the face of increasing afterload. This, combined with the presence of post-systolic shortening (i.e., contraction after aortic valve closure) and therefore wasted myocardial work, suggests that the acute response to an increase in afterload may be compromised in the endurance athlete's LV (Wasfy *et al.*, 2019; Shave *et al.*, 2019). Further investigation is required to confirm whether stimulus-specific exercise training to pressure or volume loading (i.e., resistance vs endurance) results in a compromised LV adaptation to respond to an increase in LV volume or pressure, respectively.

7.4.3 Endurance Exercise Elicits a Flow-Mediated Increase in Right Ventricular Afterload

The pulmonary vasculature is a high flow, low resistance circuit, comprising thin, distensible walls to facilitate diffusion across the blood-gas barrier. Whilst the pulmonary vasculature is capable of reducing its already low resistance further (via recruitment of previously unopened vessels and distension of already perfused vessels), this does not fully

compensate for the increase in flow, therefore pressure increases (La Gerche *et al.*, 2010; Wright *et al.*, 2019). Highly-trained endurance athletes, capable of achieving large cardiac outputs, therefore, can achieve profound increases in RV pressure (La Gerche *et al.*, 2010; Wright *et al.*, 2019), resulting in a disproportionate increase in RV end-systolic wall stress, in comparison to the LV (La Gerche *et al.*, 2011).

Whether repetitive exposure to high pressure leads to remodelling of the pulmonary vasculature remains unknown. Cardiorespiratory fitness has been positively associated with pulmonary vascular distensibility and increased pulmonary capillary blood volume (Lalande *et al.*, 2012). Whilst a causal effect between exercise training and pulmonary vascular adaptation has not been shown, it may be postulated that highly-trained endurance athletes have the greatest PV distensibility, which contributes to pulmonary vascular reserve capacity, and perhaps alleviating the afterload that the RV confronts. However, this hypothesis remains untested. Furthermore, maladaptive remodelling of the pulmonary vasculature in athletes has also been speculated (Domenech-Ximenos *et al.*, 2020). In animals with exceptionally high cardiac outputs relative to body mass, such as Thoroughbred race horses, the associated pressure increase in the pulmonary vasculature may be sufficient to compromise microvascular structural integrity, resulting in the eventual rupturing of the capillaries (i.e., exercise induced pulmonary haemorrhaging (West, 2000; Poole & Erickson, 2016). Whether this occurs in exercising humans, however, is debated (Hopkins, 2010; Sheel & McKenzie, 2010). However, accumulative adaptation of the blood-gas-barrier, by means of exercise-induced haemorrhaging, may result in an increased collagen deposition in the affected region, fibrosis, and perhaps diffusion limitation.

Chapter 4 shows that whilst athletes are capable of achieving higher RV pressures during intense exercise, in comparison to non-athletic controls, the increase in pressure is similar for a given increase in cardiac output (**Chapter 4;**

Table 3. Meta-analysis results comparing the weighted mean difference for right ventricular dimensions and areas between athletes and non-athletic controls.

Parameter	Study *n* (Participant *n* Control:Athlete)	MCID 0.2*SDpooled	WMD (95% CI)	Effect size Cohen's d	Z	P value	I2
RV basal diameter (mm)	19 (924:1986)	1.0	-4.7 (-5.9, -3.5)	1.0	7.77	<0.0001	86
RV mid-cavity diameter (mm)	9 (680:1137)	0.9	-5.3 (-6.9, -3.6)	1.1	6.13	<0.0001	91
RV length (mm)	12 (512:818)	1.5	-6.4 (-8.7, -4.1)	0.8	5.42	<0.0001	82
RVOT Proximal PLAX (mm)	7 (380:639)	1.0	-4 (-5, -3)	0.9	6.22	<0.0001	87
RVOT Proximal PSAX (mm)	4 (100:232)	0.9	-3 (-5, -1)	0.7	3.04	0.002	71
RVOT Distal PSAX (mm)	4 (501:884)	1.2	-3 (-3, -2)	0.4	7.26	<0.0001	89
RV EDA (ml)	15 (367:1058)	0.8	-6.5 (-9.9, -3.2)	1.9	3.8	0.0001	98
RV EDA index (ml·m2)	8 (252:303)	0.3	-1.57 (-1.85, -1.28)	0.9	10.8	<0.0001	84
RV ESA (ml)	14 (549:1362)	0.5	-3.5 (-5.4, 1.7)	1.6	3.78	0.0002	97
RV ESA index (ml·m2)	5 (84:105)	0.2	-14.4 (-16.4, -12.5)	0.8	14.47	<0.0001	29
FAC (%)	24 (848:1857)	1.2	0.60 (-0.41, 1.61)	-0.1	1.60	0.25	73

RV, right ventricle; RVOT, right ventricular outflow tract; PLAX, parasternal long axis; PSAX, parasternal short axis; EDA, end-diastolic area; ESA, end-systolic area.

Figure *19*). Furthermore, **Chapter 5** demonstrates that an increase in circulating volume, via Gelofusine infusion and subsequent passive leg raise, elicits a similar increase in RV pressure in both athletes and controls. Therefore, this thesis provides no evidence to support the presence exercise induced pulmonary vascular remodelling. The presence of pulmonary haemorrhaging and vascular fibrosis in selectively bred animal athletes, however, suggests that the pulmonary vasculature may be underbuilt for the extremes of exercise performance. Future investigation in this area should consider the effect of long-term, high volume endurance training on pulmonary vascular distensibility in i) master athletes, in whom an age-related decline in distensibility (Mackay *et al.*, 1978; Forton *et al.*, 2020) may cause an excessive flow-mediated increase in pulmonary artery pressure, and RV afterload, and ii) swimmers, in whom a central redistribution of blood volume and sympathetic excitation associated with cold water immersion increases the risk of pulmonary oedema (Moon *et al.*, 2016; Volk *et al.*, 2020).

7.5 Clinical Implications

The observations made in this thesis have clear clinical implications. A prerequisite for diagnostic utility is the ability to discriminate abnormal from normal reference ranges (Greenhalgh, 1997; Whiting *et al.*, 2003). As such, the establishment of normal reference ranges of RV function in endurance athletes will enable clinicians and physiologists to discriminate abnormal function (**Chapter 4, Table 6**). Differentiation of training-induced physiologic RV adaptations from pathologic RV myopathy is of great clinical importance in the care of athletes. The upper reference limits calculated in **Chapter 4** validate the recommended upper limit of 40 mmHg for RVSP in athletes (D'Andrea *et al.*, 2011). Additionally, it was demonstrated that resting RV function in endurance athletes is dependent upon the variable assessed (i.e., myocardial displacement, velocity, or deformation), as well as the region of the RV free wall that is examined. The data from **Chapter 4** support the implementation of a higher upper reference value for TAPSE (33

mm) beyond that previously recommended in athletes (Galderisi *et al.*, 2015); however, the upper reference value for RV S' is within the upper limits of normal for the general adult population (Rudski *et al.*, 2010). Furthermore, a slightly lower basal longitudinal strain, and an enhanced base-apex strain gradient may be considered normal functional features of the athlete's heart. The diagnostic importance of sensitive measures of myocardial function, such as deformation imaging, has recently been established for the diagnosis of arrhythmogenic right ventricular cardiomyopathy (Mast *et al.*, 2019; Claeys *et al.*, 2020). Abnormal deformation, specifically a lower deformation of the RV basal area, may help to discriminate early "subclinical stage" arrhythmogenic cardiomyopathy that is not detected by conventional approaches (Mast *et al.*, 2019). Differentiation between arrhythmogenic cardiomyopathy and normal physiologic remodelling with athletic training remains an extremely important consideration for sports cardiologists, due to the considerable morphologic overlap. Clinicians working with athletes should therefore be aware of regional free wall mechanics at rest (favouring a more dynamic apex and a less dynamic base), which may resemble that of pathology. Functional reserve during stress echocardiography may play an important role in the future as a non-invasive tool to differentiate physiological remodelling from arrhythmogenic pathology. For example, Claeys et al. (2020) recently demonstrated the considerable functional reserve of athletes and non-athletes, which is impaired in arrhythmogenic cardiomyopathic subjects. Observations made from **Chapter 5** also confirms an enhanced region-specific 'functional response' at the base of the endurance athlete's RV following haemodynamic volume perturbation.

Previous studies examining the influence of exercise training in both non-clinical and clinical populations have focused largely on markers of structural or resting functional remodelling. Many of these studies have shown little or modest adaptations to training (Dubach *et al.*, 1997; Myers *et al.*, 2002). The data from this thesis suggest the potential

for positive functional remodelling, even in the absence of marked changes in structure, in a healthy population. Accordingly, even though exercise-training interventions may not result in gross changes in myocardial architecture, it is possible that functional adaptation may reduce overall myocardial stress and could be relevant in clinical populations.

7.6 Limitations

There are some limitations of this thesis that warrant consideration. First, and foremost, the data presented in **Chapters 5 and 6** are relevant for young healthy men. Furthermore, data included in the meta-analysis presented in **Chapter 4** are largely skewed by male dominated studies and relative paucity of female-only studies. The exclusion of females from studies due to methodological complexity surrounding hormone status and known physiological sex-differences remains a widespread problem in numerous scientific fields (Elliott-Sale *et al.*, 2021). Future study should accept the challenges associated with the inclusion of females as participants to develop our understanding in this population. Additionally, studies included in the meta-analyses were largely based upon cross-sectional design. Experimental **Chapters 5 and 6** were also cross-sectional in design. As such, the findings of this thesis are relevant to athletes who have engaged in sustained exercise training (i.e., over a number of years). However, the temporal progression of exercise-induced cardiac remodelling may evoke different structural and functional adaptations (Arbab-Zadeh *et al.*, 2014; Weiner *et al.*, 2015). Furthermore, a relatively small sample size was employed for experimental **Chapters 5 and 6.** Nonetheless, both chapters were sufficiently powered to detect differences in myocardial function when haemodynamics were provoked via intravenous volume infusion and leg press exercise at a power of 0.95 and a one-tailed alpha of 0.05.

Athletes included in experimental **Chapters 5 and 6** did not show extensive structural cardiac remodelling, which was likely influenced by the exclusion of

'competitive athletes' that were subject to doping control; the experimental procedure used (i.e., intravenous Gelofusine infusion), is considered a prohibited substance by the World anti-Doping Agency. However, the fact that trained individuals did not have marked structural remodelling specifically enabled us to investigate potential functional remodelling in the absence of structural remodelling. It is possible that a different or exaggerated adaptation may occur in athletes with greater training volume or intensity (i.e., dose) or more substantial cardiac remodelling. Further investigation of sport-specific LV and RV functional adaptation is warranted in a larger cohort and should be further considered in athletes with substantial cardiac remodelling.

Isometric exercise was performed without a Valsalva manoeuvre in order to facilitate echocardiography data collection; however, this is unlikely to fully reflect the 'typical' training conditions of resistance athletes. In contrast to this study design, the experimental design of Haykowsky et al. (2001) assessed the LV specifically during the Valsalva manoeuvre, demonstrating an absence of transmural wall stress due to concomitant increase in intrathoracic pressure and arterial pressure. The findings from Haykowsky et al. (2001), i.e., absence of an increase in transmural LV wall stress, have largely been accepted; however, the haemodynamic load on the LV for many resistance sports is not confined to the haemodynamic conditions during a Valsalva manoeuvre. Rock climbing, which is associated with a sustained (~40 s) increase in systemic arterial pressure (Callender *et al.*, 2020), may provide a better model to assess the long-term adaptation to exercise-induced increases in LV afterload than conventional resistance athletes (i.e., weightlifters and body builders). Yet, cardiac structure and function has not been characterised in this rock-climbing population.

7.7 Further Study

7.7.1 Heart and lung interaction in endurance athletes: Ventricular interdependence in athletes

The present thesis examined LV and RV function at rest, and in response to specific haemodynamic perturbation. Furthermore, all echocardiographic measures were obtained at a specific point of the respiratory cycle (end-expiration). However, changes in intrathoracic pressure can have a significant effect on ventricular filling (Claessen *et al.*, 2014; Cheyne *et al.*, 2020). Moreover, since the LV and RV share the ventricular septum and are surrounded by a relatively non-distensible pericardium, rapid changes in filling in one ventricle can have a profound effect on the EDV of the other ventricle (i.e., diastolic ventricular interaction) (Belenkie *et al.*, 2001). During exercise with increasing lung volumes and greater fluctuations in intrathoracic pressure, diastolic ventricular interaction may be exaggerated and cause a leftward septal shift during diastole. Septal movement during exercise may constrain LV SV, and conceivably, may contribute to the plateau in LV SV in observed during progressive exercise. Septal flattening during exercise may become problematic if the repeated stress propagates chronic remodelling that may be maladaptive. This hypothesised increase in ventricular interaction may contribute towards the pattern of myocardial fibrosis frequently observed among endurance athletes. RV insertion point fibrosis may be present in up to 40% of athletes (La Gerche *et al.*, 2012*c*; Gati *et al.*, 2018). Repetitive and pronounced inspiratory septal flattening during exercise may, at least partly, be responsible for the prevalence of exercise-induced myocardial fibrosis which appears focal to the RV "hinge" points (Wilson *et al.*, 2011; La Gerche *et al.*, 2012*c*; Eijsvogels *et al.*, 2016; Gati *et al.*, 2018). Analysis of myocardial deformation (i.e., strain) characteristics, alongside conventional geometric and volumetric measurements, may provide further insight into the acute interventricular response and potential regional variations.

7.7.2 Sex differences in region-specific right ventricular remodelling

In **Chapter 4**, sex was not considered a significant determinant of the difference in strain values between endurance athletes and non-athletic controls. However, only two studies specifically differentiated strain values between sex specifically. Using 3D STE, Lakatos et al. (2018) demonstrated that free wall longitudinal strain was lower in female water polo athletes, which was predominantly mediated by a reduction at the basal level, synonymous with the current meta-analysis. Interestingly, these sex-specific differences were not observed in female athletes from an endurance background in an investigation by Sanz-de la Garza et al. (2017*a*) using 2D STE. It has been demonstrated that RV strain is consistently elevated in females across all segments (Muraru *et al.*, 2016). Further study is therefore required to identify the influence of sex on training-induced functional remodelling of the RV; it is possible that, as with structural remodelling of the LV (Howden *et al.*, 2015), functional adaptation associated with dynamic exercise is blunted in females.

7.8 Conclusions

Collectively, the results from the three studies within this thesis demonstrates a functional adaptation of the athlete's heart, characterised by an enhanced functional response to specific haemodynamic load. The divergent LV functional response to an increase in pressure or volume, in resistance and endurance athletes, respectively, in the absence of overt structural remodelling, is intriguing and builds upon our understanding of the athlete's heart. The mechanisms which underpin these functional adaptations warrants further investigation. The observation of a widened base-to-apex RV strain gradient and associated region-specific functional response at the base of the endurance athlete's RV upon volume manipulation, highlights that the RV functional adaptation should be considered alongside structure in the clinical evaluation of the athlete's heart. The clinical impact of such information is clear, with improved clinical utility in the diagnostic differentiation of pathological and physiological remodelling.

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Appendices

List of Appendices:

Appendix I: Publications During PhD Candidature (April 2016 -2021)

Appendix II: Supplementary Material for Chapter 4

Appendix III: Supplementary Material for Chapter 5

Appendix IV: Supplementary Material for Chapter 6

Appendix V: Ethical Approval for Chapter 4 - Meta-Analysis

Appendix VI: Prospero Registration for Chapter 4 - Meta-Analysis

Appendix VII: Ethical Approval Chapter 5 and 6

Appendix VIII: Journal Articles Specifically Relating to this Thesis

Appendix I: Publications During PhD Candidature (April 2016 -2021)

Articles in peer-reviewed journals (n = 18)

1. **Dawkins TG**, Curry BA, Wright S, Meah V, Yousef Z, Eves N, Shave R, Stembridge M. (2021). Right ventricular function and region-specific adaptation in athletes engaged in high-dynamic sports: A meta-analysis. *Circulation: Cardiovascular Imaging*

2. **Dawkins TG** & Curry BA. (2019). Respiratory muscle training in spinal cord injury: a breath of fresh air for the heart. *J Physiol* **597,** 5533-5534.

3. **Dawkins TG,** Curry BA, Drane AL, Lord RN, Richards C, Brown M, Pugh CJA, Lodge F, Yousef Z, Stembridge M & Shave RE. (2020). Stimulus-specific functional remodeling of the left ventricle in endurance and resistance-trained men. *Am J Physiol Heart Circ Physiol* **319,** H632-H641.

4. **Dawkins TG**, Shave RE, Baggish AL, Drane AL, Parisi EJ, Roberts MG & Roberts JD. (2019). Electrocardiographic changes following six months of long-distance triathlon training in previously recreationally active individuals. *Eur J Sport Sci*, 1-10.

5. Ewalts M, **Dawkins T**, Boulet LM, Thijssen D & Stembridge M. (2020). The influence of increased venous return on right ventricular dyssynchrony during acute and sustained hypoxaemia. *Exp Physiol*.

6. Gibbons TD, Tymko MM, Thomas KN, Wilson LC, Stembridge M, Caldwell HG, Howe CA, Hoiland RL, Akerman AP, **Dawkins TG**, Patrician A, Coombs GB, Gasho C, Stacey BS, Ainslie PN & Cotter JD. (2020). Global REACH 2018: The influence of acute and chronic hypoxia on cerebral haemodynamics and related functional outcomes during cold and heat stress. *J Physiol* **598,** 265-284.

7. Lord RN, Wakeham DJ, Pugh CJA, Simpson LL, Talbot JS, Lodge FM, Curry BA, **Dawkins TG**, Shave RE & Moore JP. (2020). The influence of barosensory vessel mechanics on the vascular sympathetic baroreflex: insights into aging and blood pressure homeostasis. *Am J Physiol Heart Circ Physiol* **319,** H370-H376.

8. Perkins D, **Dawkins T** & Stembridge M. (2018). Early exercise for lifelong benefit: sustained cardiac programming in rats and the potential translation to humans. *J Physiol* **596,** 1135-1136.

9. Simpson LL, Meah VL, Steele A, Thapamagar S, Gasho C, Anholm JD, Drane AL, **Dawkins TG**, Busch SA, Oliver SJ, Lawley JS, Tymko MM, Ainslie PN, Steinback CD, Stembridge M & Moore JP. (2020). Evidence for a physiological role of pulmonary arterial baroreceptors in sympathetic neural activation in healthy humans. *J Physiol* **598,** 955-965.

10. Simpson LL, Meah VL, Steele AR, Gasho C, Howe CA, **Dawkins TG**, Busch SA, Oliver SJ, Moralez G, Lawley JS, Tymko MM, Vizcardo-Galindo GA, Figueroa-Mujica RJ, Villafuerte FC, Ainslie PN, Stembridge M, Steinback CD & Moore JP.

(2021). Global REACH 2018: Andean highlanders, chronic mountain sickness and the integrative regulation of resting blood pressure. *Exp Physiol* **106,** 104-116.

11. Steele AR, Tymko MM, Meah VL, Simpson LL, Gasho C, **Dawkins TG**, Villafuerte FC, Ainslie PN, Stembridge M, Moore JP & Steinback CD. (2020). Global REACH 2018: renal oxygen delivery is maintained during early acclimatization to 4,330 m. *Am J Physiol Renal Physiol* **319,** F1081-F1089.

12. Stembridge M, Williams AM, Gasho C, **Dawkins TG,** Drane A, Villafuerte FC, Levine BD, Shave R & Ainslie PN. (2019). The overlooked significance of plasma volume for successful adaptation to high altitude in Sherpa and Andean natives. *Proc Natl Acad Sci U S A* **116,** 16177-16179.

13. Talbot JS, Lord RN, Wakeham DJ, **Dawkins TG**, Curry BA, Brown M, Lodge FM & Pugh CJA. (2020). The influence of habitual endurance exercise on carotid artery strain and strain rate in young and middle-aged men. *Exp Physiol* **105,** 1396-1407.

14. Tymko MM, Hoiland RL, Tremblay JC, Stembridge M, **Dawkins TG**, Coombs GB, Patrician A, Howe CA, Gibbons TD, Moore JP, Simpson LL, Steinback CD, Meah VL, Stacey BS, Bailey DM, MacLeod DB, Gasho C, Anholm JD, Bain AR, Lawley JS, Villafuerte FC, Vizcardo-Galindo G & Ainslie PN. (2021). The 2018 Global Research Expedition on Altitude Related Chronic Health (Global REACH) to Cerro de Pasco, Peru: an Experimental Overview. *Exp Physiol* **106,** 86-103.

15. Wakeham DJ, Lord RN, Talbot JS, Lodge FM, Curry BA, **Dawkins TG**, Simpson LL, Shave RE, Pugh CJA & Moore JP. (2019). Upward resetting of the vascular sympathetic baroreflex in middle-aged male runners. *Am J Physiol Heart Circ Physiol* **317,** H181-H189.

16. Wright SP, **Dawkins TG**, Eves ND, Shave RE, Tedford R & Mak S. (2020). Hemodynamic Function of the Right Ventricular-Pulmonary Vascular-Left Atrial Unit: Normal Responses to Exercise in Healthy Adults. *Am J Physiol Heart Circ Physiol*.

17. **Dawkins, T. G.,** Shave, R. E., Baggish, A. L., Drane, A. L., Parisi, E. J., Roberts, M. G., & Roberts, J. D. (2020). Electrocardiographic changes following six months of long-distance triathlon training in previously recreationally active individuals. *Eur J Sport Sci, 20*(4), 553-562. doi:10.1080/17461391.2019.1641556

18. Roberts, J. D., Suckling, C. A., Peedle, G. Y., Murphy, J. A., **Dawkins, T. G.,** & Roberts, M. G. (2016). An Exploratory Investigation of Endotoxin Levels in Novice Long Distance Triathletes, and the Effects of a Multi-Strain Probiotic/Prebiotic, Antioxidant Intervention. *Nutrients, 8*(11). doi:10.3390/nu8110733

Articles under review or in submission (n = 8)

1. Steele AR, Tymko MM, Meah VL, Simpson LL, Gasho C, **Dawkins TG**, Villafuerte FC, Ainslie PN, Stembridge M, Moore JP & Steinback CD. (2021). Global REACH 2018: Volume regulation in high-altitude Andeans with and without chronic mountain sickness. *Am J Physiol Renal Physiol*

2. Wakeham, D., Lord, R., Talbot, J., Lodge, F., Curry, B. A., **Dawkins, T. G.**, Simpson, L., Pugh, C., Shave, R. & Moore, J, P. No relationship between muscle sympathetic vasomotor outflow and aortic systolic pressure augmentation in young or middle-aged normotensive men

3. Wakeham, D., Lord, R., Talbot, J., Lodge, F., Curry, B. A., **Dawkins, T. G.**, Simpson, L., Pugh, C., Shave, R. & Moore, J, P. The influence of habitual endurance exercise and age on the sympathetic and haemodynamic responses during isolated metaboreflex activation in normotensive men

4. **Dawkins, T. G.,** Curry, B. A., Drane, A., Lord, R., Richards, C., Lodge, F., Yousef, Z., Pugh, C., Shave, R. & Stembridge, M. Evidence of region-specific right ventricular functional adaptation in endurance trained men in response to an acute volume infusion

5. Kelly, T., Brown, C., Bryant-Ekstrand, M., Lord, R., **Dawkins, T**., Drane, A., Barak, O., Dragun, T., Duke, J.W., Foster, G.E., Dujic, Z. & Lovering, A. Cardiopulmonary responses of breath hold divers to isocapnic hypoxia is not altered by sildenafil administration.

6. Hansen A, Moralez G, Amin SB, Simpson LL, Hofstatter F, Anholm JD, Gasho C, Stembridge M, **Dawkins TG,** Tymko MM, Ainslie P, Villafuerte FC, Romero SA & Hearon CM. (Submitted). Global Reach 2018: The adaptive phenotype to life with polycythemia. *PNAS*.

7. Stembridge M, Hoiland R, Williams A, Howe C, Donnelly J, **Dawkins T**, Drane A, Tymko M, Gasho C, Anholm J, Simpson L, Moore J, Bailey D, Macleod D & Ainslie P. (Submitted). Temporal differences in hypoxic pulmonary vasoconstriction in response to combined hemodilution and arterial hypoxemia. *Chest*.

8. Hansen A, Moralez G, Amin SB, Simpson LL, Hofstatter F, Anholm JD, Gasho C, Stembridge M, **Dawkins TG,** Tymko MM, Ainslie P, Villafuerte FC, Romero SA & Hearon CM. (Submitted). Global Reach 2018: Andeans with chronic mountain sickness have a hypertensive response to exercise unrelated to changes in muscle sympathetic nerve activity. *The Journal of Physiology.*

Book Chapters

Dawkins, T. G. (2016) 'Transition', in Smith, G. and Roberts, J. Triathlon – it HURTS: Inspiring stories on the path to becoming an ironman (2014). London: Matador, pp. 31-38

Oral Presentations Specific to this Thesis

Dawkins, T.G., Curry, B., Lord, L., Richards, C., Drane, A. L., Lodge, F., Shave, R. E. and Stembridge, M., (2019). Global and Regional Right Ventricular Deformation in Endurance Athletes Following Acute Volume Loading. Accepted for presentation to the 3rd *Pan Wales Sport and Exercise Sciences Conference*.

Dawkins, T.G. (2019) Athlete's Heart: Cardiac Response to Volume Infusion in Endurance and Resistance-Trained Athletes. Invited Presentation for *Wales Exercise Medicine Symposium*.

Dawkins T.G., Curry BA, Drane AL, Lord RN, Richards C, Brown M, Pugh CJA, Lodge F, Yousef Z, Stembridge M & Shave RE. Evidence of region-specific right ventricular functional adaptation in endurance trained men in response to an acute volume infusion *The 4th Okanagan Cardiovascular & Respiratory Symposium*, Okanagan, British Columbia, March 2020. (Postponed due to Covid-19).

Other Oral Presentations

Dawkins, T.G., Shave, R.E., Baggish, A.L., Drane, A.L., Roberts, M.G. and Roberts, J.D., (2018). Electrocardiographic Changes Following Six-Months of Endurance Training in Previously Training-Naïve Individuals. Accepted for presentation to *The 3rd Okanagan Cardiovascular & Respiratory Symposium*, Okanagan, British Columbia.

Dawkins, T.G., Gibbons, T., Tymko, M. M., Cotter, J. D., Ainslie, P. N., Shave, R. E. and Stembridge, M. (2018). Interaction between core temperature and acute hypoxia on pulmonary arterial pressure. *Annual Academic Associate Poster Symposium*

Successful Grant Funding
- **2017 - £5840** - Recipient of **Santander Scholarship** funding (£4840) and **Gilchrist Foundation** funding (£1000) for research expenses and consumables towards: *The 2018 Global Research Expedition on Altitude Related Chronic Health (GLOBAL REACH) to Cerro de Pasco, Peru.*
- **2016-2021 - £25,000.** Awarded the PhD **Bursary Programme** from Cardiff Metropolitan University**.**
- **2020 - £500**. Recipient of '**Go Global'** travel funding for the personal development of research techniques in neuromuscular physiology. Principal Investigator: Dr Craig Steinback (University of Alberta, Canada).
- **2019 - £5600** '**Short Term Mobility Funding'** to support myself and four students to present at the 2020 Okanagan Cardiovascular and Respiratory Symposium and to conduct research with Prof. Neil Eves (University of British Columbia, Canada): *Inspiratory heart and lung interaction in endurance athletes.*
- **2019 - £500**. '**Go Global'** funding to support travel to the University of Split, Croatia, to provide echocardiographic expertise for the study: *Is blood flow through IPAVA and PFO related to breath-hold and SCUBA diving-induced pulmonary hypertension?* Principal Investigator*:* Dr Andrew Lovering.
- **2018 - £500**. Recipient of **The Physiology Society** travel grant for the personal development of research techniques in cerebrovascular physiology with Prof. Phil Ainslie (University of British Columbia, Canada).
- **2018 - £500**. Recipient of '**Go Global'** travel grant to learn novel cardiopulmonary research techniques with Prof. Neil Eves (University of British Columbia, Canada) and contribute to the research project entitled: *Heart-lung interactions and the effect on cardiac and vascular mechanics.*

Total: £ 15,940

Right ventricular function and region-specific adaptation in athletes

engaged in high-dynamic sports: A meta-analysis

This Appendices includes:

Supplementary Figure 1 - 8

Supplementary Table 1 – 4

Study	Athlete Type	Male (%)	Sample size (n) Control	Sample size (n) Athlete	Mean Age (Years) Control	Mean Age (Years) Athlete
Bohm 2016	Elite master endurance athletes	CT: 100; A: 100	33	33	46	47
Caso 2002	Competitive swimmers	Not stated	20	20	21	22
Claeys 2020	Regular endurance athlete	CT: 100; A: 100	20	20	37	34
D'Andrea 2013	Swimmers, runners, soccer & basketball	CT: 61; A: 61	230	395	25.2	28.8
D'Andrea 2020	Swimmers, runners & cyclists	CT: 57; A: 59	150	350	32.4	31.6
D'Ascenzi 2013	Professional soccer, basketball & volleyball	CT: 64; A: 76	78	100	25.9	25.2
Doronina 2018	Water polo (national team)	CT: 0; A: 0	15	15	23	24
Esposito 2014	Competitive rowers	CT: 100; A: 100	43	40	29	28.4
King 2013	Elite rowers	CT: 100; A: 100	17	18	27.1	22.4
Kooreman 2019	College rowers, lacrosse, water polo	CT: 0; A: 0	31	37	19	19
Krol 2011	Olympic team rowers, speed-skating & cycling	CT: 80; A: 84	41	38	24.3	25.1
LaGerche 2015	Cyclists and runners	CT: 86; A: 84	7	10	34	35
Lakatos 2018 (F)	Water polo (national team)	CT: 0; A: 0	20	30	19.5	19
Lakatos 2018 (M)	Water polo (national team)	CT: 100; A: 100	20	30	19.9	18.9
Leischik 2016	Triathletes	CT: 0; A: 0	37	33	31.2	34.3
Lewicka Potocka 2020	Marathon runners	CT: 100; A: 100	15	34	40.2	39.9
Major 2015	Endurance athletes	CT: 100; A: 100	25	52	26.5	24.6
Malmgren 2015	Competitive handball players	CT: 0; A: 0	33	33	23	20
Owen 2004	Runners	CT: 100; A: 100	40	21	40	39
Popovic 2011	Elite water polo	CT: 100; A: 100	20	21	21.4	21.5
Popple 2018	Elite soccer players	CT: 100; A: 100	20	100	25	25
Randers 2013	Danish national soccer players	CT: 0; A: 0	25	11	29.3	24
Rimensberger 2014	Ultra-endurance runners	CT: 100; A: 100	33	26	41	44
Sanchis Gomar 2016	Elite runners & cyclists	CT: 100; A: 100	18	11	54	58
Simsek 2013	Long-distance runners	CT: 27; A: 27	30	44	23.8	24.1
Sitges 2017	Professional mid-high dynamic sportsmen	CT: 100; A: 100	50	100	25	26
Teske 2009	Elite cyclists, runners & rowers	CT: 59; A: 70	61	63	27.7	27
Utomi 2015	Elite ultra-endurance runners	CT: 100; A: 100	21	19	27	34
Zha 2015 †	Marathon runners	CT: 53; A: 53	24	19	45	32.4

WMD (95% CI)	-1.8 mm (-1.1, -2.5)
Effect size d (MCID)	0.4 (0.7 mm)
Mean Control	23.5 mm
Mean Athlete	25.3 mm
P value	P = 0.0001
I² (%)	84
Egger's Test	1.19 (P = 0.245)

Supplementary Figure 1. Individual forest plots showing weighted mean difference (WMD) and 95% confidence intervals for individual studies included in meta-analysis of tricuspid annular plane systolic excursion (TAPSE). ‡ indicates that numerical data were retrieved from graphical format using a reliable open source software programme. MCID, minimum clinically important difference.

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Study	Athlete Type	Male (%)	Sample size (n) Control	Athlete	Mean Age (Years) Control	Athlete
Baggish 2010	Elite rowers	CT: 100; A: 100	20	20	21	25
Bohm 2016	Elite master endurance athletes	CT: 100; A: 100	33	33	46	47
Caso 2002	Competitive swimmers	Not stated	20	20	21	22
D'Andrea 2007	Competitive master athletes	CT: 100; A: 100	25	40	47.4	48.2
D'Andrea 2013	Swimmers, runners, soccer and basketball	CT: 61; A: 61	230	395	25.2	28.8
D'Andrea 2020	Swimmers, runners & cyclists	CT: 57; A: 59	150	350	32.4	31.6
D'Ascenzi 2013	Professional soccer, basketball & volleyball	CT: 64; A: 76	78	100	25.9	25.2
Doronina 2018	Water polo (national team)	CT: 0; A: 0	15	15	23	24
Esposito 2014	Competitive rowers	CT: 100; A: 100	43	40	29	28.4
Hedman 2015	Competitive high-dynamic athletes	CT: 0; A: 0	48	46	21	21
Krol 2011	Olympic team rowers, speed-skating, cycling	CT: 80; A: 84	41	38	24.3	25.1
LaGerche 2010	Endurance athletes	CT: 87; A: 90	15	40	36	38
LaGerche 2015	Cyclists & runners	CT: 86; A: 84	7	10	34	35
Lakatos 2018 (F)	Water polo (national team)	CT: 0; A: 0	20	30	19.5	19
Lakatos 2018 (M)	Water polo (national team)	CT: 100; A: 100	20	30	19.9	18.9
Major 2015	Endurance athletes	CT: 100; A: 100	25	52	26.5	24.6
Malmgren 2015	Competitive handball players	CT: 0; A: 0	33	33	23	20
Molmen 2012 ‡	Master cross-country ski athletes	CT: 100; A: 100	10	11	71.7	74.3
Moro 2013	Competitive cyclists	CT: 100; A: 100	36	17	30.7	25.7
Ong 2017	NHL hockey players	CT: 100; A: 100	592	26	19	18
Pagourelias 2013	Elite endurance cyclists	CT: 100; A: 100	26	80	26.6	31.2
Poh 2008	Speed skaters	CT: 58; A: 67	14	24	24	22
Popovic 2011	Elite water polo	CT: 100; A: 100	20	21	21.4	21.5
Popple 2018	Elite soccer players	CT: 100; A: 100	20	100	25	25
Rimensberger 2014	Ultra-endurance runners	CT: 100; A: 100	33	26	41	44
Sanchis Gomar 2016	Elite runners and cyclists	CT: 100; A: 100	18	11	54	58
Sanz delaGarza 2017 (F)	Runners	CT: 0; A: 0	20	20	36.9	37.4
Sanz delaGarza 2017 (M)	Runners	CT: 100; A: 100	20	20	36.2	38
Simsek 2013	Long-distance runners	CT: 27; A: 27	30	44	23.8	24.1
Stewart 2020	Cyclists, runners, swimmers & rowers	CT: 100; A: 100	30	30	29	31
Teske 2009	Elite cyclists, runners & rowers	CT: 59; A: 70	61	63	27.7	27
Tumuklu 2008	Competitive soccer players	CT: 100; A: 100	20	24	26.5	25.2
Utomi 2015	Elite ultra-endurance runners	CT: 100; A: 100	21	19	27	34
Zha 2015 †	Marathon runners	CT: 53; A: 53	24	19	45	32.4

RV S' (cm·s⁻¹) — Mean Difference IV, Random, 95% CI

Greater than Control — Lower than Control

WMD (95% CI)	-0.7 cm·s⁻¹ (-0.3, -1.1)
Effect size d (MCID)	0.4 (0.4 cm·s⁻¹)
Mean Control	12.9 (cm·s⁻¹)
Mean Athlete	13.5 (cm·s⁻¹)
P value	P = 0.001
I² (%)	86
Egger's Test	0.61 (P = 0.548)

Supplementary Figure 2. Individual forest plots showing weighted mean difference (WMD) and 95% confidence intervals for individual studies included in meta-analysis of right ventricular tricuspid annular myocardial velocity. ‡ indicates that numerical data were retrieved from graphical format using a reliable open source software programme. MCID, minimum clinically important difference.
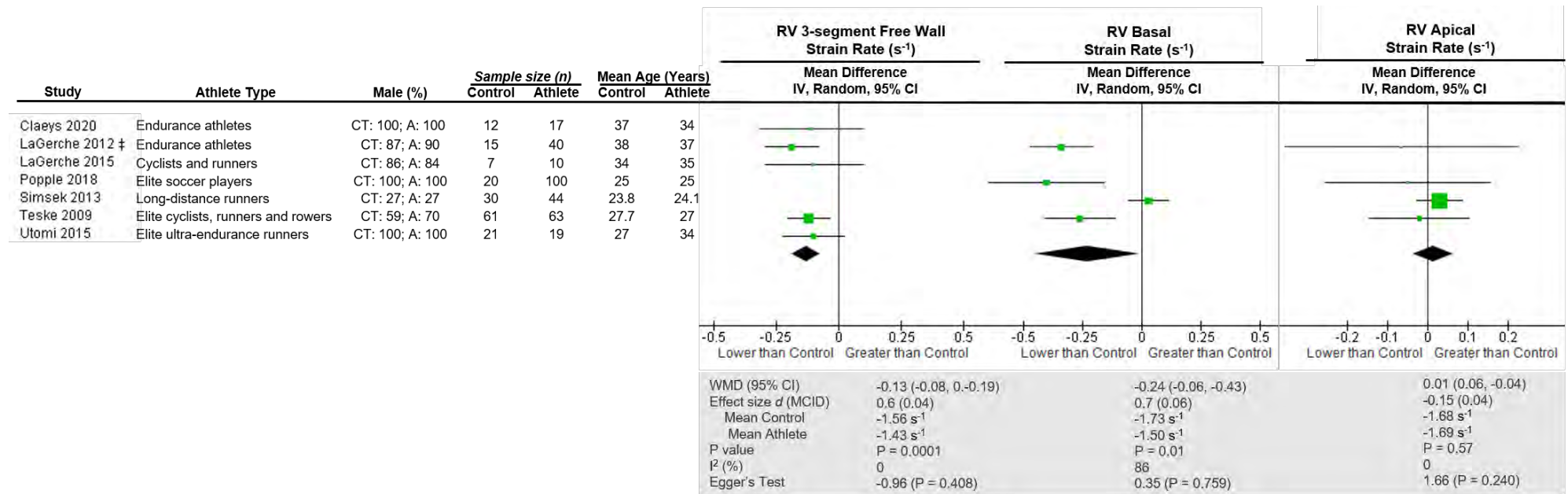
Supplementary Figure 3. Individual forest plots showing weighted mean difference (WMD) and 95% confidence intervals for individual studies included in meta-analysis of right ventricular free-wall strain rate. † denotes that strain values were obtained via magnetic resonance imaging. ‡ indicates that numerical data were retrieved from graphical format using a reliable open source software program. MCID, minimum clinically important difference.
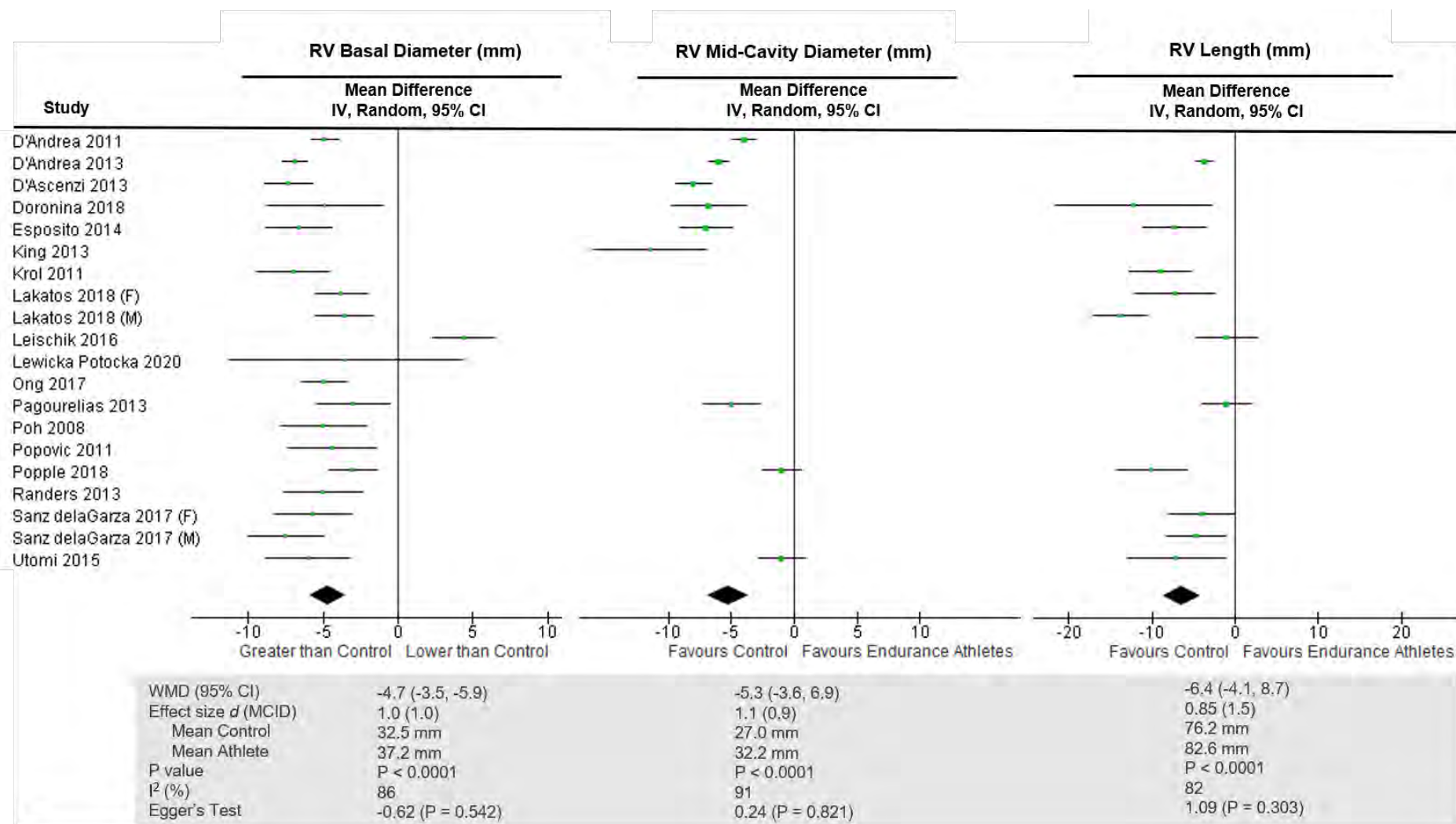
Supplementary Figure 4 Individual forest plots showing weighted mean difference (WMD) and 95% confidence intervals for individual studies included in meta-analysis of right ventricular dimensions. MCID, minimum clinically important difference.
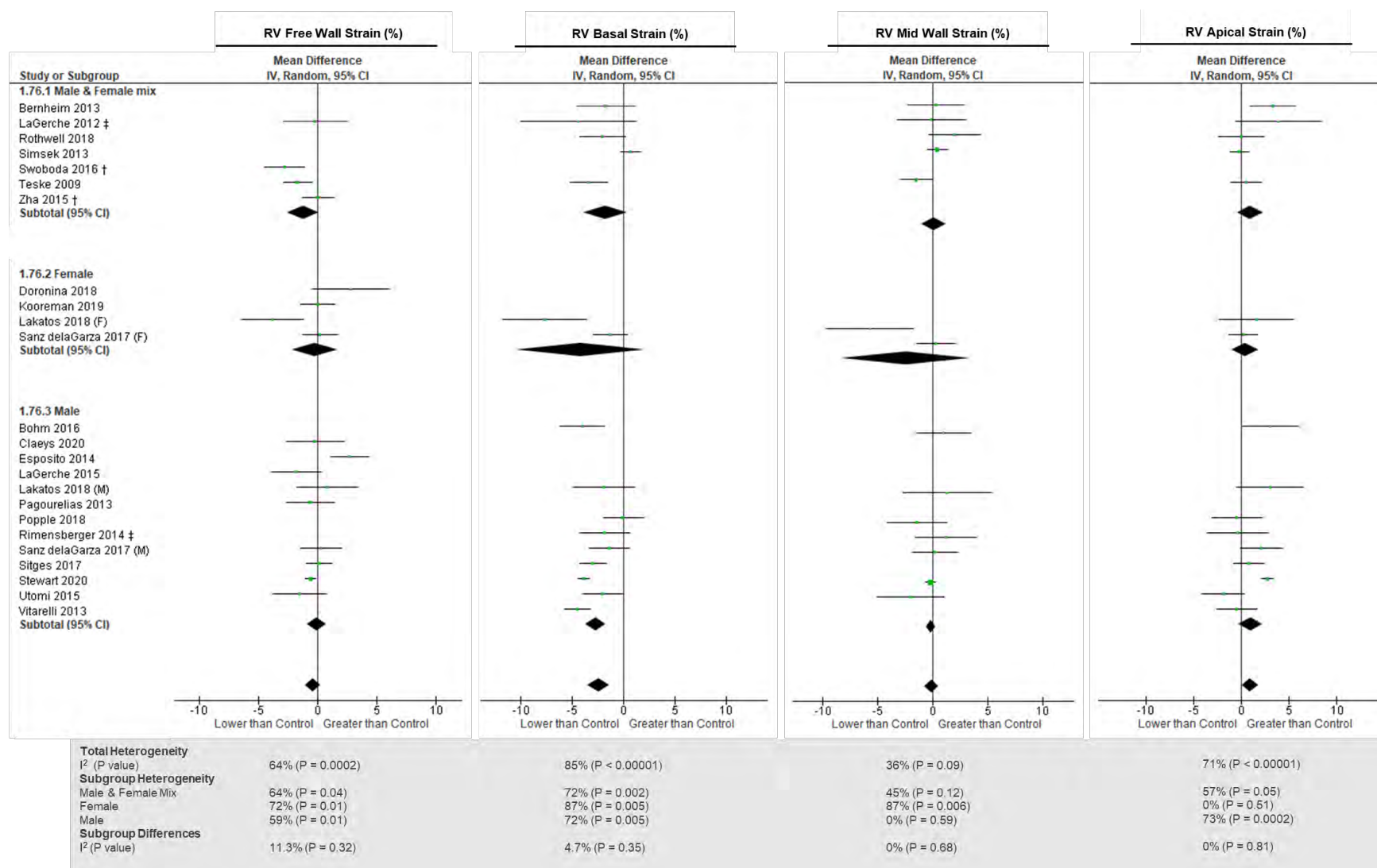
Supplementary Figure 5. Forest plot showing meta-analysis of athlete-control differences in right ventricular (RV) strain parameters, categorised by sex.
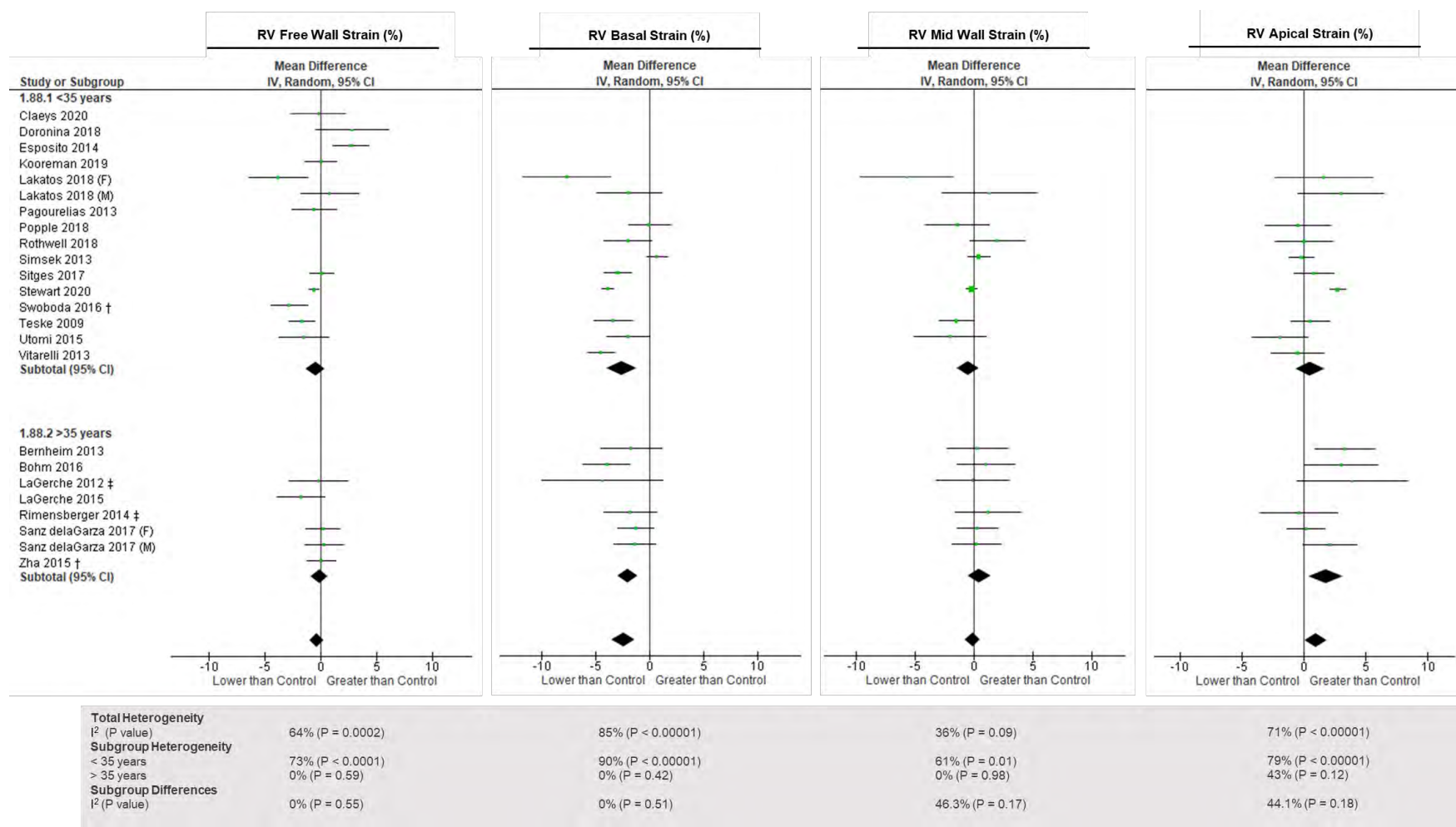
Supplementary Figure 6. Forest plot showing meta-analysis of athlete-control differences in right ventricular (RV) strain parameters, categorised by age.
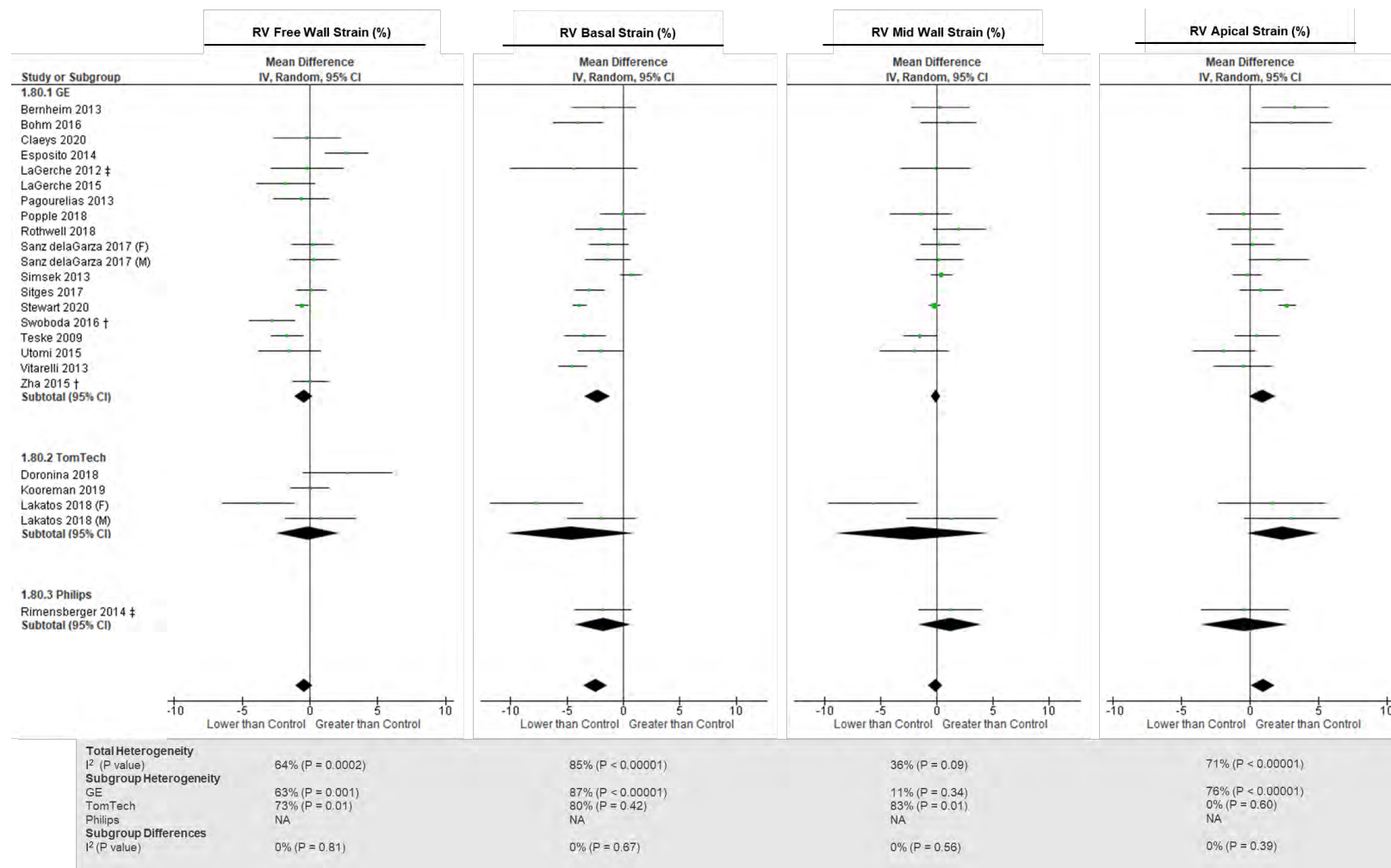
Supplementary Figure 7. Forest plot showing meta-analysis of athlete-control differences in right ventricular (RV) strain parameters, categorised by vendor.
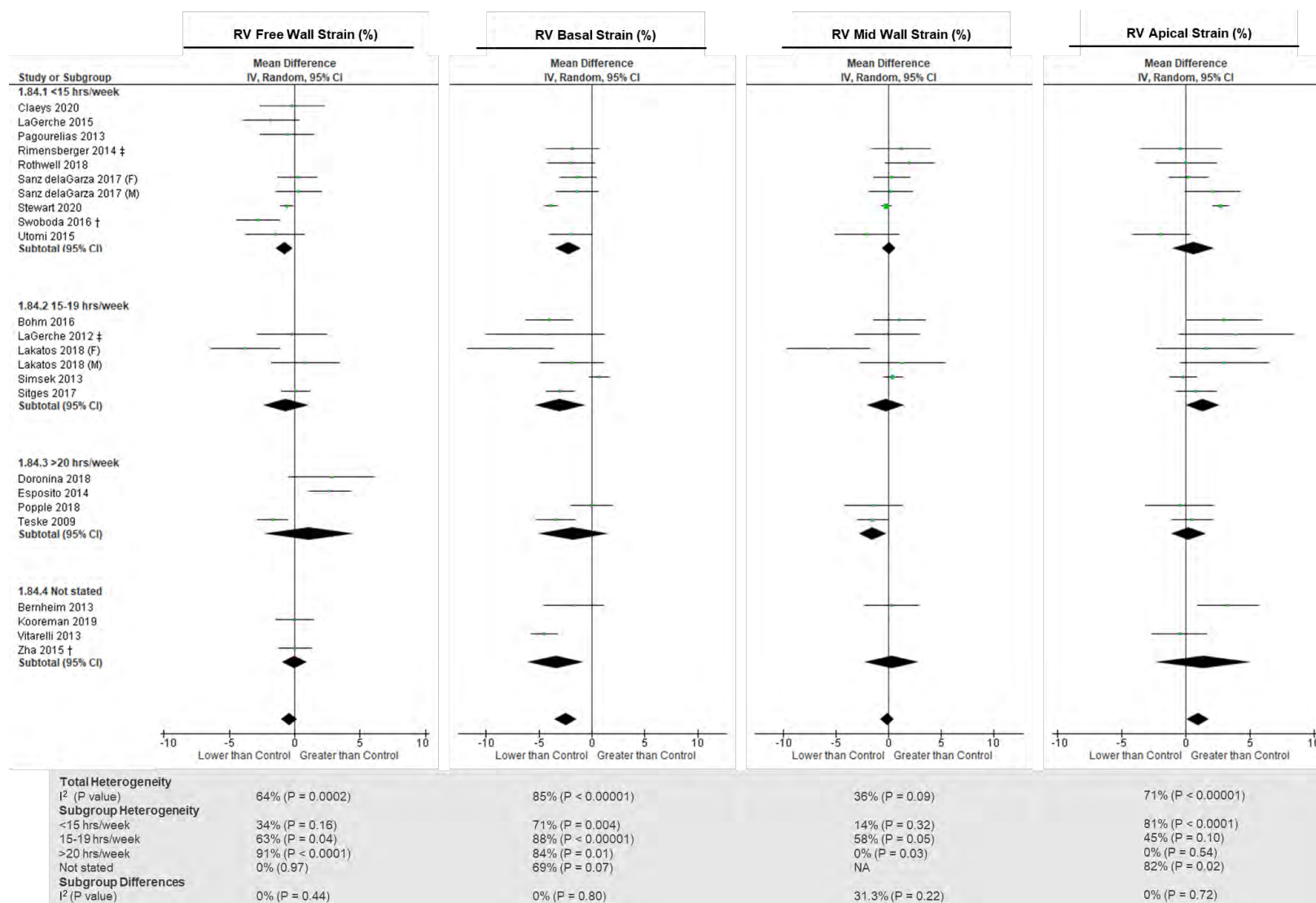
Supplementary Figure 8. Forest plot showing meta-analysis of athlete-control differences in right ventricular (RV) strain parameters, categorised by weekly training hours.

Supplementary Table 1 – Primary RV parameters extracted for meta-analyses and unique study identification number. Details of missing data are provided for each parameter, where information has been provided within individual studies.

Study	RVSP rest	RVSP exercise	TAPSE	S'	RV free Wall Strain	RV regional strain	RV free wall strain rate	RV regional strain rate	Activity levels and exclusion criteria for Control population	PMID / DOI
Baggish 2010						YES			≤ 1 h/week No history of CVD	19997021 / DOI: 10.1249/MSS.0b013e3181c81604
Bernheim 2013						YES			Not engaged in regular sporting activities No personal history of CVD, no family history if SCD or inherited disease	22790189 / DOI: 10.1016/j.ijcard.2012.06.074
Bohm 2016			YES	YES		YES			≤ 3 h/week No history of CPD	27073129 DOI: 10.1161/CIRCULATIONAHA.115.020975
Bossone 1999	YES	YES							Normally active	10334439 / DOI: 10.1016/s0735-1097(99)00055-8
Caso 2002			YES	YES	YES				Untrained Excluded for: coronary artery, valvular and congenital heart disease, heart failure, cardiomyopathy, arterial hypertension, and diabetes mellitus	12106860 / DOI: 10.1016/s0002-9149(02)02453-0
Claessen 2016	YES A: 18/19 C: 8/9	YES A:13/19 C:6/9							Healthy non-athletes	26508387 / DOI: 10.1016/j.jcmg.2015.06.018
Claeys 2020	YES	YES	YES				YES		≤ 3 h/week No history of CVD and no evidence of CV pathology on echo and ECG	31578557 / DOI: 10.1093/ehjci/jez228
DAndrea 2007				YES					Sedentary Without CV structural and functional abnormalities	16959340 / DOI: 10.1016/j.ijcard.2006.03.041
DAndrea 2011	YES			YES					Without CV structural and functional abnormalities	20864610 / DOI: 10.1378/chest.10-1260

Study									Population	Reference
DAndrea 2013	YES			YES					Sedentary Without CV structural and functional abnormalities	21737163 / DOI: 10.1016/j.ijcard.2011.06.058
D'andrea 2020	YES	YES	YES	YES					Normotensive, normal ECG, normal LV EF (>55%)	32367187 / DOI: 10.1007/s10554-020-01871-z
DAscenzi 2013				YES					Recreational activities No CV structural or functional abnormalities	22588713 / DOI: 10.1007/s10554-012-0063-z
Doronina 2018			YES	YES	YES				≤ 3 h/week No uncommon echo and/or ECG changes	DOI:10.1155/2018/3561962
Esposito 2014	YES A: 22/40 C: 11/43		YES	YES	YES				Sedentary Free of cardiac disease, medication and abusive substance	24373023 / DOI: 10.1111/echo.12499
Hedman 2015				YES					Normally active	27900120 / DOI: 10.1136/bmjsem-2015-000015
King 2013	YES		YES		YES				Non-athlete	23488623 / DOI: 10.1111/echo.12153
Kooreman 2019			YES		YES				≤ 2 h/week Normal AHA 12-point assessment, no family history of CVD	31033616 / DOI: 10.1097/JSM.0000000000000501
Krol 2011	YES A: 23/38 C: 28/41			YES					Sedentary No known CVD or pulmonary disease	21615486 / DOI: 10.1111/j.1540-8175.2011.01437.x
Kuchynka 2010	YES A: 51/51 C: 44/47								Not regularly engaged in sporting activities	19765071 / DOI: 10.1111/j.1540-8175.2009.00965.x
La Gerche 2010	YES	YES		YES					Mean 70 ± 25 min/week No CV symptoms or risk factors	20724567 / DOI: 10.1152/japplphysiol.00457.2010
La Gerche 2012					YES	YES	YES	YES	≤ 3 h/week No known CVD, symptoms or risk factors	22192334 / DOI: 10.1016/j.echo.2011.11.023
La Gerche 2015	YES	YES	YES	YES	YES			YES	≤ 3 h/week	26038590 / DOI: 10.1093/eurheartj/ehv202

Study									Population	PMID / DOI
									No known CVD, symptoms or risk factors	
Lakatos 2018 (F)			YES	YES	YES	YES			≤ 3 h/week No uncommon echo or ECG changes	30216120 / DOI: 10.1152/ajpheart.00304.2018
Lakatos 2018 (M)			YES	YES	YES	YES			≤ 3 h/week No uncommon echo or ECG changes	30216120 / DOI: 10.1152/ajpheart.00304.2018
Leischik 2016			YES A: 37/37 C: 31/33						Policewomen VO_{2max} 26.9 ± 6.1 ml/kg^{-1}/min^{-1}	27207600 / DOI: 10.1177/0031512516650461
Lewicka Potocka 2020			YES						Sedentary No chronic disease	31909474 / DOI: 10.5603/CJ.a2019.0110
Major 2015			YES	YES					≤ 3 h/week Normotensive, no history of CV risk factors	25804387 / DOI: 10.1556/APhysiol.102.2015.1.2
Malmgren 2015			YES	YES					≤ 2 h/week No CVD	25600906
Mansencal 2007 (F)	YES								≤ 3 h/week No previous history of heart disease or hypertension	17719301 / DOI: 10.1016/j.ahj.2007.04.056
Mansencal 2007 (M)	YES								≤ 3 h/week No previous history of heart disease or hypertension	17719301 / DOI: 10.1016/j.ahj.2007.04.056
Molmen 2012				YES					No participation in regular endurance training in previous 2 years	22273242 / DOI: 10.3109/14017431.2012.660192
Moro 2013				YES					Not involved in regular physical activity "healthy"	23478754 / DOI: 10.12659/MSM.883829
Ong 2017				YES					Recreational sport activities	28477859 / DOI: 10.1016/j.amjcard.2017.03.042
Owen 2004			YES						Sedentary No history or symptoms of CVD	15193825 / DOI: 10.1016/j.ijcard.2003.07.008

Study									Criteria	Reference
Pagourelias 2013	YES			YES	YES				≤ 3 h/week Free from known CVD, family history of cardiomyopathy and medication or illicit drugs	23978677 / DOI: 10.1016/j.echo.2013.07.019
Poh 2008				YES					≤ 3 h/week No CV structural or functional abnormalities and free from medication	17602763 / DOI: 10.1016/j.ijcard.2007.04.051
Popovic 2011			YES	YES					≤ 2 h/week No CVD, diabetes, renal disease, infection, smoking, or anabolic steroid use	21904284 / Not available
Popple 2018			YES	YES		YES		YES	≤ 3 h/week Free from known CVD, diabetes, or renal disease	30102797 / DOI: 10.1111/sms.13272
Randers 2013			YES A: 11/27 C: 25/28						Untrained	23829646 / DOI: 10.1080/02640414.2013.792950
Rimensberger 2014	YES		YES	YES		YES			Median 3 h/week Normotensive without history of CVD, no medication or ergogenic aid	24357641 / DOI: 10.1136/bjsports-2013-092859
Rothwell 2018			YES	YES		YES		YES	< 2 h/week Non-smokers, free from known cardiovascular, renal, liver, endocrinal, metabolic or respiratory disease.	29305036 / DOI: 10.1016/j.echo.2017.11.021
Sanchis Gomar 2016	YES		YES	YES					≤ 3 training sessions/week No major risk factors, metabolic, or CVD, COPD, renal or hepatic failure, or cancer	27494731 / DOI: 10.1016/j.ijcard.2016.07.197

Study									Criteria	PMID / DOI
Sanz de la Garza 2017 (F)				YES	YES	YES			≤ 3 h/week No known CVD, symptoms or risk factors for CVD	28150069 / DOI: 10.1007/s00421-017-3546-8
Sanz de la Garza 2017 (M)				YES	YES	YES			≤ 3 h/week No known CVD, symptoms or risk factors for CVD	28150069 / DOI: 10.1007/s00421-017-3546-8
Simsek 2013			YES	YES		YES		YES	Sedentary Not involved in exercise program	23478892 / DOI: 10.1007/s10554-013-0204-z
Sitges 2017			YES		YES	YES			≤ 2 h/week No heart disease	27848162 / DOI: 10.1007/s10554-016-1014-x
Stewart 2020				YES	YES	YES			Recreational sport (VO_{2peak} <50 ml/kg^{-1}/min^{-1}) "healthy" nonsmokers, no history of cardiopulmonary, metabolic, or neuromuscular disorder and not taking medication	32175971 / DOI: 10.1249/MSS.0000000000002336
Swoboda 2016					YES				≤ 3 h/week Without medical condition or contraindication to CMR	27535657 / DOI: 10.1186/s12968-016-0266-x
Teske 2009			YES	YES	YES	YES	YES	YES	≤ 3 h/week No history of heart disease, normal ECG and BP	19240064 / DOI: 10.1093/eurheartj/ehp040
Tran 2019	YES	YES							Nonathletes Not on beta-blockers and without arrhythmias, or mitral valve prosthesis	31652633 / DOI: 10.3390/jcm8101756
Tumuklu 2008				YES					No regular physical exercise "healthy"	17410479 / DOI: 10.1007/s10554-007-9218-8
Utomi 2015	YES		YES	YES	YES	YES	YES		≤ 3 h/week Non-smokers, free from known CVD, without early family history of CVD and not taking medication	25779702 / DOI: 10.1007/s00421-015-3147-3

Vitarelli 2013	YES						YES			Sedentary Free of heart and systemic disease and not taking medication.	23299399 / DOI: 10.1093/ehjci/jes298
Wright 2019	YES	YES								≤ 30 mins exercise, 3 times per week Excluded if history of CVD, diabetes, or pulmonary, hepatic, metabolic, systemic, neuromuscular or malignant disease	29878071/ DOI: 10.1093/cvr/cvy138
Zha 2015			YES	YES	YES					No aerobic training No history of CVD and not taking medication	26664880 / DOI: 10.3389/fcvm.2015.00008

A and C denote the sample size for the given variable / the total sample size, for Athletes and Controls, respectively. CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; SCD, sudden cardiac death.

Supplementary Table 2. Comparison of weighted mean differences (WMD) and standard mean differences (SMD).

Parameter	WMD (95% CI)	P value	SMD (95% CI)	P value
RV free wall strain (%)	-0.4 (-1.0, 0.2)	0.22	-0.1 (-0.3, 0.1)	0.22
RV basal strain (%)	-2.5 (-3.5, -1.4)	<0.00001	-0.7 (-1.0, -0.4)	<0.00001
RV mid-wall strain (%)	0.0 (-0.7, 0.6)	0.89	0.0 (-0.2, 0.2)	0.90
RV apical strain (%)	0.9 (0.1, 1.8)	0.04	0.27 (0.03, 0.51)	0.03
RV free wall strain rate (%)	-0.13 (-0.08, -0.19)	<0.00001	-0.56 (-0.81, -0.31)	<0.0001
RV basal strain rate (s^{-1})	-0.26 (-0.06, -0.46)	0.01	-0.84 (-1.39, -0.28)	0.003
RV mid-wall strain rate (s^{-1})	-0.13 (-0.25, 0.00)	0.04	-0.44 (-0.83, -0.05)	0.03
RV apical strain rate (s^{-1})	-0.02 (0.05, -0.09)	0.57	-0.10 (-0.32, 0.12)	0.36
RVSP rest (mm Hg)	2.9 (1.3, 4.5)	0.0005	0.5 (0.3, 0.8)	0.0003
RVSP exercise (mm Hg)	11.0 (6.5, 15.6)	<0.00001	1.2 (1.7, 0.7)	<0.00001
TAPSE (mm)	-1.8 (-1.0, -2.5)	<0.0001	-0.4 (-0.6, -0.2)	<0.0001
RV S' (cm·s^{-1})	-0.7 (-0.3, -1.1)	0.001	-0.4 (-0.6, -0.2)	0.0003

TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; S', peak systolic annular velocity of the right ventricle.

Criteria	Claessen 2015	Bossone 1999	Bernheim 2013	Baggish 2010	Bohm 2016	Caso 2002	Claeys 2020	D'Andrea 2007	D'andrea 2011	D'Andrea 2020	D'Andrea 2013	D'Ascenzi 2013	D'Silva 2020	Dorinina 2018	King 2013
Supplementary Table 3. Quality assessment of studies within the meta-analysis using the National Institute of Health (NIH) quality assessment tool of observational cohort and cross-sectional studies (criteria are defined in the table footer)															
1	yes	yes	yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	yes	yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	yes	yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	yes	yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	no	no	No	no	No	No	Yes	No	No	No	No	No	No	No	No
6	no	no	No	no	No	No	No	No	No	No	No	No	Yes	No	No
7	no	no	No	no	No	No	No	No	No	No	No	No	Yes	No	No
8	yes	no	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	no	no	No	no	No	No	No	No	No	No	Yes	No	No	No	No
10	yes	yes	yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	no	no	No	Yes	Yes	No	No	No	Yes	No	Yes	Yes	No	No	No
12	no	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes	NA	NA
13		no	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Yes	No
Quality Rating (Good, Fair or Poor)	Fair	Fair	Fair	Good	Good	Fair	Good	Fair	Good	Fair	Good	Good	Fair	Fair	Fair

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Criteria	Kooreman 2019	Krol 2011	Kuchynka 2010	La Gerche 2012	La Gerche 2015	La Gerche 2010	Leischik 2016	Lewicka Potoka 2020	Major 2015	Malmgren 2015	Manenscal 2007	Moro 2013	Ong 2017
Supplementary Table 3 continued.													
1	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No
2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	No	No	No	No	No	No	No	No	No	No	No	No	No
6	No	No	No	No	No	No	No	No	No	No	No	No	No
7	No	No	No	No	No	No	No	No	No	No	No	No	No
8	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
9	No	No	No	No	No	No	No	No	No	No	No	No	No
10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
11	Yes	No	No	Yes	No	Yes	No	No	No	No	Yes	No	No
12	NA	NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA
13	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Quality Rating (Good, Fair or Poor)	Good	Fair	Fair	Good	Fair	Good	Poor	Poor	Poor	Fair	Fair	Fair	Fair

Supplementary Table 3 continued.														
Criteria	Owen 2004	Pagourelias 2013	Sanchis 2016	Sanz de la Garza 2017	Simsek 2013	Sitges 2017	Stewart 2020	Swoboda 2016	Teske 2009	Tran 2019	Utomi 2015	Vitarelli 2013	Zha 2015	Hedman 2015	Molmen 2012
1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No
6	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
7	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
8	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
9	No	No	Yes	Yes	No	No	No	No	Yes	No	No	No	No	No	Yes
10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes
12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
13	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes		Yes	Yes	Yes	Yes	No
Quality Rating (Good, Fair or Poor)	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair

Criteria	Esposito 2014	Tumuklu 2008	Poh 2008	Popovic 2011	Popple 2018	Randers 2013	Rimensberger 2014	Rothwell 2018	Wright 2019
Supplementary Table 3 continued.									
1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	No	No	No	No	No	No	No	No	No
6	No	No	No	No	No	No	No	Yes	Yes
7	No	No	No	No	No	No	No	Yes	Yes
8	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
9	No	No	No	No	No	Yes	No	No	No
10	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	No	Yes	No	Yes	No	No	Yes	No	Yes
12	NA	NA	NA	NA	NA	NA	NA	NA	NA
13	Yes	No	No	Yes	Yes	No	Yes	Yes	No
Quality Rating (Good, Fair or Poor)	Fair	Fair	Fair	Fair	Fair	Fair	Good	Fair	Good

NA, not applicable

Criteria:

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? (Cross-sectional = no)
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? (Cross-sectional = no)
8. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
9. Was the exposure(s) assessed more than once over time?
10. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
11. Were the outcome assessors blinded to the exposure status of participants?
12. Was loss to follow-up after baseline 20% or less? (NA if cross sectional)
13. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Supplementary Table 4. PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1 & 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6 (Figure 2 & 4; Table 2)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6 (Figure 2 & 4; Table 2)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6 (Figure 2 & 4; Table 2)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6 (Figure 2 & 4; Table 2)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

For more information, visit: **www.prisma-statement.org**.

Evidence of region-specific right ventricular functional adaptation in endurance-trained men in response to an acute volume infusion

This Appendices includes:

    Supplementary Table – 7 - 8

Supplementary Table 7. Percent change in primary variables from baseline in response to 7 ml·kg^{-1} intravenous Gelofusine infusion and subsequent passive leg raise (mean ± SD). Not age corrected.

Variable, %	Infusion		Passive Leg Raise		ANCOVA
	Controls (*n* = 11)	Endurance-trained (*n* = 13)	Controls (*n* = 11)	Endurance-trained (*n* = 13)	(*P* value)
RVSP	25 ± 24	16 ± 15	27 ± 28	21 ± 19	0.216
RVD Base	4 ± 7	1 ± 9	5 ± 9	3 ± 8	0.909
RVD mid-wall	3 ± 11	3 ± 14	1 ± 8	3 ± 13	0.292
RVD length	2 ± 4	3 ± 4	2 ± 3	4 ± 4	0.480
RV area diastole	8 ± 18	7 ± 14	5 ± 13	7 ± 13	0.528
RV area systole	10 ± 27	6 ± 14	6 ± 13	6 ± 16	0.819
RV FAC	1 ± 9	2 ± 13	0 ± 9	3 ± 14	0.632
RV S'	14 ± 13	-3 ± 13	13 ± 14	2 ± 10	0.216
TAPSE	7 ± 8	6 ± 8	7 ± 7	7 ± 9	0.737
RVFWSL	8 ± 9	6 ± 10	6 ± 10	5 ± 10	0.793
Basal RVFWSL	5 ± 12	17 ± 15	4 ± 11	15 ± 19*	**0.041**
Apical RVFWSL	11 ± 13	4 ± 15	10 ± 15	5 ± 16	0.404

RVSP, right ventricular systolic pressure; RVFWSL, right ventricular free-wall longitudinal strain; RVFW SR, right ventricular free-wall longitudinal strain rate.

* *P* < 0.05 significant difference between groups.

Supplementary Table 8. RV functional response to 7 ml·kg^{-1} intravenous Gelofusine infusion and subsequent passive leg raise. Data presented as mean ± SD (95% confidence intervals).

| Variable	Baseline		Infusion		Passive Leg Raise	
	Non-Athlete Controls	Endurance Athlete	Non-Athlete Controls	Endurance Athlete	Non-Athlete Controls	Endurance Athlete
RV Longitudinal Strain Characteristics						
RV FWSL (%)	-25.4 ± 2.9 (23.7 – 27.1)	-26.3 ± 2.2 (25.1 – 27.5)	-27.2 ± 2.9 (25.6 – 28.9)	-27.8 ± 2.5 (26.5 – 29.1)	-26.8 ± 2.8 (25.1 – 28.4)	-27.5 ± 3.1 (25.9 – 29.2)
RV Basal FWSL (%)	-21.9 ± 3.6 (19.8 – 24.1)	-21.2 ± 3.5 (-19.3 – 23.1)	-23.2 ± 5.0 (-20.2 – 26.1)	-24.4 ± 2.9† (-22.9 – -26.0)	-22.8 ± 4.2 (20.3 – 25.3)	-23.9 ± 3.0 (22.3 – 25.5)
RV Apical FWSL (%)	-25.4 ± 4.7 (22.6 – 28.1)	-26.8 ± 3.6 (24.8 – 28.7)	-27.9 ± 4.2 (25.4 – 30.4)	-27.8 ± 4.8 (25.2 – 30.4)	-27.6 ± 4.7 (24.8 – 30.3)	-27.9 ± 5.0 (25.2 – 30.7)

RVFWSL, right ventricular free-wall longitudinal strain

Stimulus-specific functional remodelling of the left ventricle in endurance and

resistance-trained men

This Appendices includes:

Supplementary Figure 9 - 10
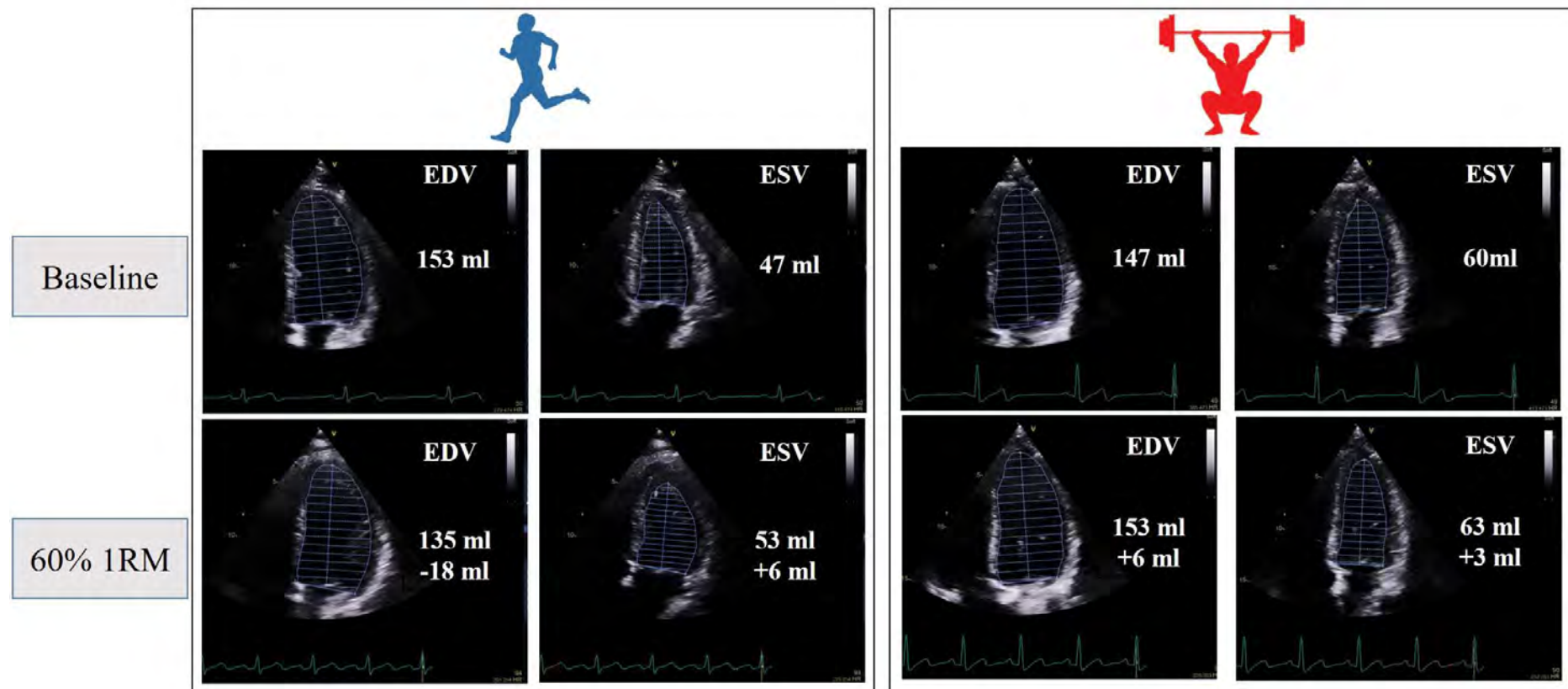
Supplementary Figure 9: Representative two-dimensional image of the left ventricle in the apical four chamber view demonstrating a relative preservation of both end-diastolic volume (EDV) and end-systolic volume (ESV) in resistance athletes during leg-press exercise at 60% 1 repetition maximum.
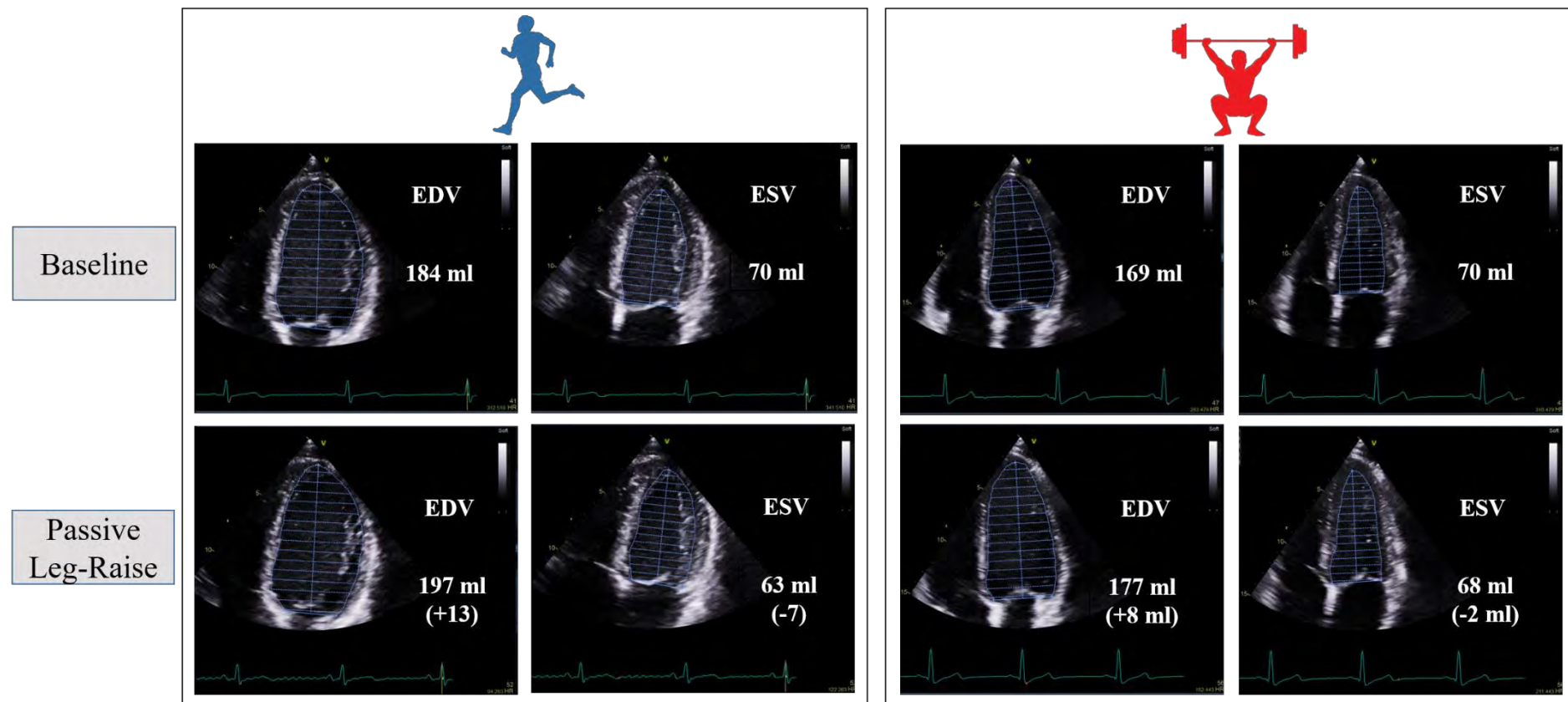
Supplementary Material Figure 10: Representative two-dimensional image of the left ventricle in the apical four chamber view demonstrating an increase in end-diastolic volume (EDV) during passive leg-raise after 7 ml·kg^{-1} intravenous Gelofusine infusion in both endurance and resistance-trained athletes

Appendix V: Ethical Approval for Chapter 4 - Meta-Analysis

APPLICATION FOR ETHICS APPROVAL

When undertaking a research or innovation project, Cardiff Met staff and students are obliged to complete this form in order that the ethics implications of that project may be considered.

The document *Ethics application guidance notes* will help you complete this form and is available from the Ethics Governance Section of the Cardiff Met website. The School or Unit in which you are based may also have produced some guidance documents which you can access via your supervisor or School Ethics Coordinator.

PLEASE NOTE:
Participant recruitment or data collection MUST NOT commence until ethics approval has been obtained.

PART ONE

1A: GENERAL INFORMATION	
Name of applicant:	Tony Dawkins
Supervisor (if student project):	Dr Mike Stembridge
School / Unit:	School of Sport and Health Sciences
Student number (if applicable):	SM21593
Programme enrolled on (if applicable):	PhD (Part Time)
Project Title: If using a working title, it should convey what the project is about	Right ventricular function and region-specific adaptation in athletes: A meta-analysis
Expected start date of data collection:	N/A
Approximate duration of data collection:	N/A
Funding Body (if applicable):	N/A
Other researcher(s) working on the project If your collaborators are external to Cardiff Met, include details of the organisation they represent	Bryony Curry PhD Student University of British Columbia - Okanagan Professor Rob Shave Director of the School of Health and Exercise Sciences University of British Columbia - Okanagan
Will the study involve NHS patients or staff? If yes, attach a copy of your NHS application to this form	No
Will the study involve human samples and/or human cell lines?	No

1B: Does your project fall entirely within one of the following categories:	
Desk based, involving only documents and not involving the collection of data from participants	Yes
Laboratory based, not involving human participants, human samples, animals or animal derived material	No

Application for ethics approval © Ilsw-xxx xxxx

Practice based not involving human participants (eg curatorial, practice audit)	No

Answering YES to any of these questions indicates that the project does not include any participants and you will not therefore be collecting participant data.

If this is the case, please provide a short (150 words) non-technical summary of the project, complete the Declaration at the bottom of the form and forward this form to your School Ethics Committee (or equivalent).

No further information regarding your project is required and you do not need to complete any more sections of this form.

If you have answered NO to all of these questions, please proceed to 1C.

Provide a non-technical summary of the project below:

Structural remodelling of the right ventricle (RV) in response to exercise-training has been widely evidenced in athletes. Functional adaptation of the RV, however, is less well understood. During exercise, pressure within the RV increases within the RV [1], owing to an increase in blood flow and downstream blood pressure [2]. This may result in a sustained elevation in RV pressure at rest in athletes [3, 4, 5]; although this finding has not been consistently reported [6, 7, 8, 9]. Accordingly, functional adaptation is likely to occur within the RV in response to exercise. Consistent with structural remodelling, functional adaptation may also be region-specific, affecting the base (top) and the apex (bottom) of the RV differently [10]. Consequently, the aims of this meta-analysis are to investigate the influence of chronic exercise training on (i) RVSP at rest and during exercise and (ii) global and regional RV free-wall functional adaptation between athletes and controls.

1C: Does your project fall entirely within one of the following categories:	
Compulsory projects in professional practice (eg Initial Teacher Education)	No
A project for which NHS approval has been obtained NB If this is the case, please ensure that you submit copies of the following with this form: • any questionnaires to be used • participant consent / asset form and withdrawal form • participant information sheets	No
A project which is not compulsory in professional practice and has gained external ethics approval from a body other than the NHS. NB If this is the case, please ensure that you submit a copy of the approved ethics application with this form.	No

If you have answered YES to any of these questions, please provide a short (150 words) non-technical summary of the project and complete the rest of Part One of this form. You do not need to complete Part Two.

Forward your completed form, along with any additional documents required (as indicated above) to your School Ethics Committee (or equivalent).

If you have answered NO to all of these questions, please complete the rest of this form including Part Two.

Provide a non-technical summary of the project below:

1D: DATA COLLECTION AND STORAGE	
What types of data will you collect or create?	

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APPLICATION FOR ETHICS APPROVAL

How will you manage access to and security of the data?

Will the data collected be subject to the data retention protocols of any of the following bodies?
- Human Tissue Authority (HTA)
- Health and Care Research Wales (HCRW)
- Applications involving the NHS which will be submitted via IRAS

Yes ☐

For any project which is subject to the data retention protocols of an external body listed, you must develop a data storage plan to be submitted alongside this document for consideration by your School or Unit Ethics Panel.

No ☐

Please confirm that the data collected will be stored in a manner which complies with Cardiff Met requirements via one of the following statements.

STATEMENT 1: FOR STUDENTS ON TAUGHT COURSES I confirm that any non-anonymised data related to research participants will only be stored on OneDrive, or by agreement with supervising staff, on Figshare, and that all data held elsewhere will be deleted, unless it is anonymised.	☐
STATEMENT 2: FOR STAFF APPLYING ON BEHALF OF STUDENTS ON TAUGHT COURSES I confirm that all students covered by this application are aware of their obligation to ensure that non-anonymised data related to research participants must only be stored on their Cardiff Met student OneDrive account and that all data held elsewhere must be deleted, unless it is anonymised.	☐
STATEMENT 3: FOR RESEARCH STUDENTS AND STAFF I confirm that any non-anonymised data related to research participants will be stored in a secure manner (using a platform such as OneDrive or FigShare) and that all data held elsewhere will be deleted unless it is anonymised.	☐

DECLARATION:

I confirm that this project conforms with the Cardiff Met Research Integrity & Governance Framework

I confirm that I will abide by the Cardiff Met requirements regarding confidentiality and anonymity when conducting this project.

STUDENTS: I confirm that I will not disclose any information about this project without the prior approval of my supervisor.

Signature of the applicant:	Date: 02.12.2020
FOR STUDENT PROJECTS ONLY	
Name of supervisor: Dr Mike Stembridge	Date: 02.12.2020

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Signature of supervisor:

Research Ethics Committee use only	
Decision reached: Approved	
Project reference number: PGR-3419	
Name: Rachel Lord	Date: 07/12/2020
Details of any conditions upon which approval is dependant: Click here to enter text.	

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PART TWO

If you haven't already done so elsewhere on this form, in the box below, provide a short (150 words), non-technical summary of the project.
Structural remodelling of the right ventricle (RV) in response to exercise-training has been widely evidenced in athletes. Functional adaptation of the RV, however, is less well understood. During exercise, pressure within the RV increases within the RV [1], owing to an increase in blood flow and downstream blood pressure [2]. This may result in a sustained elevation in RV pressure at rest in athletes [3, 4, 5], although this finding has not been consistently reported [6, 7, 8, 9]. Accordingly, functional adaptation is likely to occur within the RV in response to exercise. Consistent with structural remodelling, functional adaptation may also be region-specific, affecting the base (top) and the apex (bottom) of the RV differently [10]. Consequently, the aims of this meta-analysis are to investigate the influence of chronic exercise training on (i) RVSP at rest and during exercise and (ii) global and regional RV free-wall functional adaptation between athletes and controls.

A RESEARCH DESIGN

A1 Will you be using an approved protocol in your project?	No
A2 If yes, please state the name and code of the approved protocol to be used	

A3 Describe the research design to be used in your project
In this section, include details (as appropriate) of:
- Research method(s);
- Sample and sampling;
- Participants including recruitment methods, activities to be undertaken, time commitment, details of any proposed payments;
- Analytical techniques

If your project does involve the use of an approved protocol, much less details will be required but you should indicate which areas of the project are covered by the protocol.

Protocol

This meta-analysis will be registered *a priori* with PROSPERO, the international prospective register of systematic reviews and conducted in accordance with PRISMA guidelines [11]. The PRISMA checklist will be completed to ensure that essential criteria are fulfilled (Appendix).

Search strategy and inclusion criteria

The participants, interventions, comparisons, outcomes, and study design (PICOS) framework was used to guide this study.

Participants

The population of interest are athletes (aged ≥ 18 years) from sports with a high-dynamic component, as defined by the Mitchell criteria (i.e., regular contraction of large muscle groups and sustained increase in oxygen consumption) [12].

Intervention

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¹ An Approved Protocol is one which has been approved by Cardiff Met to be used under supervision of designated members of staff. For details of protocols in use in your School or Unit, contact your Ethics Coordinator

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No intervention required.

Comparison

The comparator was a non-athletic control group (aged ≥ 18 years), without history or evidence of current or chronic cardiovascular, respiratory or metabolic disease.

Outcome variables

Primary outcome variables include right ventricular systolic pressure (RVSP) obtained by non-invasive echocardiography or invasively by right-heart catheterisation, i) at rest, and ii) in response to dynamic exercise matched to an absolute or relative exercise intensity between groups. Other measures of RV systolic function obtained at rest include tricuspid annular plane systolic excursion (TAPSE), systolic myocardial velocities (S'), and measures of free-wall and regional (base and apex) strain and strain rate; obtained via echocardiography or cardiac magnetic resonance imaging (cMRI). RV free-wall strain will be defined as the arithmetic mean of the three segments of the RV free-wall.

Study design

Original publications written in English will be included. Reviews, editorials, case reports, letters to the editor and unpublished data will be excluded. Studies of longitudinal and cross-sectional design are eligible to be included, providing the training intervention was greater than 2 years in duration and the weekly training volume greater than 6 hours.

Information sources

Publicly available databases (PubMed, MEDLINE, Scopus, Science Direct and Web of Science) will be searched using the following search string: *"Right ventric* OR pulmonary arter.* OR pulmonary pressure AND function* OR strain OR mechanics OR adaptation OR remodel* OR response OR exercise OR deformation* AND athlete OR endurance."* Reference lists from included articles will also be examined in order to identify any additional relevant studies. Authors will be contacted for data and/or methodological clarification if necessary.

Study review and data extraction

Titles and abstracts of identified publications will be screened using an online reviewing software (Covidence, Veritas Health Innovation Ltd, Australia). Full text articles will be retrieved for studies that are considered relevant from the initial evaluation. Full text articles will independently assessed for eligibility against PICOS inclusion criteria by two reviewers (TGD and BAC); conflicts will be resolved through discussion or by a third reviewer (MS).

Age, sex, training status and training mode of participants will be recorded, and measures of RVSP and RV function will be extracted. Where strain is acquired using both speckle tracking echocardiography (STE) and Doppler echocardiography, only STE derived strain data will be extracted. Where athletes are reported by sex, studies will be subcategorised as males (M) and females (F), providing relevant control populations are included. If relevant data are included in graphical format, numerical data will be retrieved using a reliable open source software programme

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(WebPlotDigitizer, version 4.3 [13]). Data presented as median and range will be transformed to mean and standard deviation (SD) [14, 15]. Data presented as mean and confidence interval (CI) will be transformed to mean and SD using the following formula: $SD = \sqrt{n} \times$ (Upper limit of CI − Lower limit of CI)/3.92.

Statistical Analyses

Meta-analyses will be computed using the DerSimonian and Laird method [16], and applied to all continuous primary variables to determine the weighted mean difference (WMD) and 95% CI between control participants and athletes. A random-effects model will be implemented, based upon an *a priori* decision reflecting the anticipated heterogeneity of the data, owing to the potential variety of sporting disciplines, athletic training status (i.e., training type, volume, intensity and load), and methodological differences in data acquisition. Between-study heterogeneity will be evaluated using Chi-squared (χ^2) with a *P* value < 0.05 indicating significant heterogeneity, and the percentage of variability in the effect estimates that was due to heterogeneity evaluated using the inconsistency index (I^2) [17]. Publication bias will be assessed using funnel plots and the Egger regression method for statistically testing asymmetry, with a *P* value < 0.1 considered significant for asymmetry [18]. Forest plots will be created using Review Manager (RevMan [Computer program] Version 5.4, The Cochrane Collaboration, 2020).

A4 Will the project involve deceptive or covert research?	No
A5 If yes, give a rationale for the use of deceptive or covert research	

A6 Will the project have security sensitive implications?	No
A7 If yes, please explain what they are and the measures that are proposed to address them	

B PREVIOUS EXPERIENCE

B1 What previous experience of research involving human participants relevant to this project do you have?

I have been involved in numerous research projects resulting in 13 research publications, including three first author publications [19, 20, 21].

B2 Student project only

What previous experience of research involving human participants relevant to this project does your supervisor have?

Dr Mike Stembridge has a wealth of experience as an integrative physiologist, having published over 60 research outputs, including a meta-analysis investigating the male athlete's heart [22].

Prof Rob Shave has published over 150 research outputs, including several meta-analyses in cardiovascular research [22, 23, 24, 25, 26]

C POTENTIAL RISKS

C1 What potential risks do you foresee?

Include details of risks to the participants, the researcher and the project as a whole.

Documents relating to this meta-analysis are published already in the public domain, therefore risks relating to confidentiality and informed consent are not an issue. However, ethical issues may arise in relation to a lack of methodological rigor when collecting, summarising and integrating large amounts of data (Brown and Hedges).

  a) A lack of vigilance when carrying out the analyses may lead to inappropriate conclusions.
  b) A decision to include or exclude a study can raise ethical issues unless the criteria have been made transparent and are uniformly applied to studies.
  c) Publication bias may influence the results and therefore conclusion of a meta-analysis.

C2 How will you deal with the potential risks?

Brown and Hedges, therefore suggest that three recommendations be followed when conducting and reporting meta-analyses:

  a) Extraction and analyse the data accurately

Two investigators (TD and BC) will be responsible for the screening and extraction of data, independently. Conflicts will be resolved by a third reviewer (MS). Forest plots will be created using Review Manager (RevMan [Computer program] Version 5.4, The Cochrane Collaboration, 2020), a recognised meta-analysis software, and will be carefully reviewed by all authors.

  b) Inclusion and exclusion criteria should be explicit and applied consistently across studies.

The study protocol will be registered a priori with PROSPERO, the international prospective register of systematic reviews. Inclusion and exclusion criteria will be clearly stated and the two reviewers (TD and BC) responsible for screening articles will ensure that criteria are applied consistently across studies. Conflicts will be resolved by a third reviewer (MS).

  c) Test for publication bias

Publication bias will be assessed using funnel plots and the Egger regression method for statistically testing asymmetry, with a P value < 0.1 considered significant for asymmetry. In the presence of low between-study heterogeneity, correction factors such as the trim and fill method will be applied. However, we anticipate a high amount of heterogeneity of the data, owing to the potential variety of sporting disciplines, athletic training status (i.e., training type, volume, intensity and load), and methodological differences in data acquisition. Therefore, in the presence of high heterogeneity, correction factors such as the trim and fill method will not be applied due to the known poor performance in the presence of between-study heterogeneity.

When submitting your application you **MUST** attach a copy of the following:

  • All information sheets
  • Consent/assent form(s)
  • Withdrawal of consent form

An exemplar information sheet, exemplar participant consent form and exemplar participant withdrawal form are available via the research section of the Cardiff Met website (see section on Ethics Governance). These are based on good practice and will be useful in the majority of cases. However, it is recognised that in some cases a project will be subject to requirements from an external body. Use of these exemplars is therefore not obligatory.

References

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2. La Gerche A, Roberts T, Claessen G. The response of the pulmonary circulation and right ventricle to exercise: exercise-induced right ventricular dysfunction and structural remodeling in endurance athletes (2013 Grover Conference series). *Pulm Circ* 2014;**4**:407-16.

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13. Jelicic Kadic A, Vucic K, Dosenovic S, et al. Extracting data from figures with software was faster, with higher interrater reliability than manual extraction. *J Clin Epidemiol* 2016;**74**:119-23.

14. Luo D, Wan X, Liu J, et al. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018;**27**:1785-805.

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21. Dawkins TG, Shave RE, Baggish AL, et al. Electrocardiographic changes following six months of long-distance triathlon training in previously recreationally active individuals. *Eur J Sport Sci* 2020;**20**:553-62.

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Appendix VI: Prospero Registration for Chapter 4 - Meta-Analysis

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

Fields that have an asterisk (*) next to them means that they must be answered. Word limits are provided for each section. You will be unable to submit the form if the word limits are exceeded for any section. Registrant means the person filling out the form.

1. * Review title.

Give the title of the review in English

Right ventricular functional adaptation in endurance athletes: a meta-analysis

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

16/06/2020

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/12/2020

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Tony Dawkins

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr Dawkins

7. * Named contact email.

Give the electronic email address of the named contact.

tdawkins@cardiffmet.ac.uk

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

Cardiff Metropolitan University, Cyncoed Road, Cardiff, CF23 6XD

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Cardiff Metropolitan University

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation

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refers to groups or organisations to which review team members belong. NOTE: email and country now MUST be entered for each person, unless you are amending a published record.

Mr Tony Dawkins. Cardiff Metropolitan University
Miss Bryony Curry. Cardiff Metropolitan University
Professor Rob Shave. University of British Columbia
Dr Mike Stembridge. Cardiff Metropolitan University

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

Not applicable

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. NOTE: email and country must be completed for each person, unless you are amending a published record.

Dr Stephen Wright. University of British Columbia

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

What is the effect of long-term endurance exercise training on right ventricular function at rest?

What is the effect of long-term endurance exercise training on pulmonary artery systolic pressure, both at

rest and during exercise?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

We will search the following electronic databases: MEDLINE, PubMed, ScienceDirect, Scopus,

SPORTDiscus, Web of Science. Search not limited by date but limited to the English language. The initial

search will be extended by cross-reference of reference lists from included studies.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search results.

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Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Right ventricular function at rest and pulmonary artery systolic pressure at rest and during exercise among

endurance-trained athletes.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion: athletes endurance (endurance-trained athletes); Exclusion: cardiovascular disease

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

High dynamic sports were decided upon according to the Mitchell classification

(https://doi.org/10.1161/CIR.0000000000000237). Longitudinal training interventions were excluded if the

training programme duration was less than 6 months.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

A non-exposed control group

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Observational studies (prospective and retrospective cohort studies) are included. Grey literature, animal

studies, systematic reviews, and meta-analyses will be excluded.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

primary outcomes: right ventricular global longitudinal strain, free wall longitudinal strain, regional longitudinal

strain (base, mid and apex), tricuspid annular myocardial velocity, pulmonary artery systolic pressure or right

ventricular systolic pressure.

Quantitative analysis (meta-analyses) will be conducted if there are 2 or more studies reporting a given

outcome.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Weighted mean difference and confidence intervals

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Secondary outcomes include stroke volume, heart rate, cardiac output, right ventricular areas, volumes (end-

diastolic and systolic) and dimensions, tricuspid inflow velocity and tricuspid annular plane systolic excursion.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Weighted mean difference and confidence intervals

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

TD screened and reviewed titles and abstracts of all identified publications. Full text articles were

independently assessed for eligibility by two reviewers (TD and BC). Eligibility conflicts were resolved

through discussion or by a third reviewer (MS). Data to be extracted includes primary outcomes: right

ventricular global longitudinal strain, free wall longitudinal strain, regional longitudinal strain (base, mid and

apex), tricuspid annular myocardial velocity, pulmonary artery systolic pressure or right ventricular systolic

pressure. Secondary outcomes include stroke volume, heart rate, cardiac output, right ventricular areas,

volumes (end-diastolic and systolic) and dimensions, tricuspid inflow velocity and tricuspid annular plane

systolic excursion. Basic details including cohort size, imaging methodology (i.e. echocardiography, MRI),

pulmonary pressure methodology, body position during measurement, training volume, training history, sex

Allie cragen is ant type and fican dibas picat ply fithesd recorded using Covidence systematic review software

(Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Meta-analyses on

primary outcomes will be completed using Review Manager (RevMan) [Computer program]. Version 5.4.

Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. A final report will include a

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram detailing the

number of studies remaining after each stage of the selection process.

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Where relevant data were included in graphical format, numerical data will be retrieved using a reliable open source software programme, Plotdigitizer. Any missing statistical parameters of importance (e.g. mean and standard deviation) will be calculated if the data permits. Study investigators will be contacted for unreported or additional details, if necessary.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Study quality will be assessed by two independent reviewers using the Study Quality Assessment Tool (SQAT) for observational and cross-sectional studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Conflicts will be reviewed by a third individual.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This must not be generic text but should be specific to your review and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Quantitative analysis will be conducted if there are 2 or more studies reporting a primary outcome. If less than 2 studies report an outcome, a narrative synthesis will be included. As the meta-analysis will be based on observational data, obtained from populations which would unlikely have common variance (i.e., athletes with varying training load, athletic status, sex, and race), a random-effects model will be used. Separate random-effects meta-analyses will be applied to all outcome variables. Statistical heterogeneity will be assessed using the I^2 statistic. Results will be presented as weighted means and 95% confidence intervals. Forest plots will be presented for each meta-analysis for primary outcomes.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

Stroke volume and cardiac output will be considered as a covariate for pulmonary artery systolic pressure.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review
Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis

No

Intervention
No

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
Yes

Care of the elderly
No

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NHS
National Institute for Health Research

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care

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No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Wales

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted

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data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

Accepted for publication at Circulation: Cardiovascular Imaging

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Completed_not_published

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

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Appendix VII: Ethical Approval Chapter 5 and 6

CARDIFF METROPOLITAN UNIVERSITY

APPLICATION FOR ETHICS APPROVAL

When undertaking a research or enterprise project, Cardiff Met staff and students are obliged to complete this form in order that the ethics implications of that project may be considered.

If the project requires ethics approval from an external agency (e.g., NHS), you will not need to seek additional ethics approval from Cardiff Met. You should however complete Part One of this form and attach a copy of your ethics letter(s) of approval in order that your School has a record of the project.

The document *Ethics application guidance notes* will help you complete this form. It is available from the Cardiff Met website. The School or Unit in which you are based may also have produced some guidance documents, please consult your supervisor or School Ethics Coordinator.

Once you have completed the form, sign the declaration and forward to the appropriate person(s) in your School or Unit.

PLEASE NOTE:
Participant recruitment or data collection MUST NOT commence until ethics approval has been obtained.

PART ONE

Name of applicant:	Dr Chris Pugh
Supervisor (if student project):	N/A.
School / Unit:	Cardiff School of Sport
Student number (if applicable):	N/A.
Programme enrolled on (if applicable):	N/A.
Project Title:	The cardiovascular response to acute pressure and volume challenges in trained athletes.
Expected start date of data collection:	01/03/17
Approximate duration of data collection:	18 months.
Funding Body (if applicable):	N/A
Other researcher(s) working on the project:	Dr Mike Stembridge Miss Aimee Drane Dr Rob Shave Miss Bryony Curry Miss Megan Brown Mr Ben Bowler (MSc) Dr Zaheer Yousef Dr Freya Lodge Dr Sorayya Kakhi Mr Cory Richards (MSc)

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CARDIFF METROPOLITAN UNIVERSITY

APPLICATION FOR ETHICS APPROVAL

	Mr Tony Dawkins
Will the study involve NHS patients or staff?	Yes; the clinicians Yousef, Lodge and Kakhi are NHS employees.
Will the study involve human samples and/or human cell lines?	Yes; we will be taking a blood sample from each participant to measure haematocrit and serum sodium levels in Visit 3.

Does your project fall entirely within one of the following categories:	
Paper based, involving only documents in the public domain	No
Laboratory based, not involving human participants or human samples	No

Practice based not involving human participants (eg curatorial, practice audit)	No
Compulsory projects in professional practice (eg Initial Teacher Education)	No
A project for which external approval has been obtained (e.g., NHS)	No

If you have answered YES to any of these questions, expand on your answer in the non-technical summary. No further information regarding your project is required.
If you have answered NO to all of these questions, you must complete Part 2 of this form

In no more than 150 words, give a non-technical summary of the project
The cardiovascular system (the heart and blood vessels) undergoes structural changes in response to exercise training. It is well established that there are differences in the way in which the heart adapts to endurance and resistance based exercise training. Although both training modes elicit an increase in heart size, endurance athletes have larger cavity sizes, whereas, the hearts of resistance athletes have thicker walls. Despite these structural differences, little is known about how the function of the heart changes in response to different forms of training. Therefore, the aim of this study is to compare the cardiovascular response of endurance and resistance trained athletes to a variety of controlled physiological challenges. Specifically, we will compare stroke volume, carotid artery strain and carotid artery strain rate between three trained groups, as well as a group of sedentary individuals, in response to several challenges.

DECLARATION:
I confirm that this project conforms with the Cardiff Met Research Governance Framework

I confirm that I will abide by the Cardiff Met requirements regarding confidentiality and anonymity when conducting this project.

STUDENTS: I confirm that I will not disclose any information about this project without the prior approval of my supervisor.

Signature of the applicant:	Date:
FOR STUDENT PROJECTS ONLY	
Name of supervisor:	Date:

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Signature of supervisor:	

Research Ethics Committee use only		
Decision reached:	Project approved	☐
	Project approved in principle	☐
	Decision deferred	☐
	Project not approved	☐
	Project rejected	☐
Project reference number: Click here to enter text.		
Name: Click here to enter text.	**Date:** Click here to enter a date.	
Signature:		
Details of any conditions upon which approval is dependant: Click here to enter text.		

PART TWO

A RESEARCH DESIGN	
A1 Will you be using an approved protocol in your project?	Yes
A2 If yes, please state the name and code of the approved protocol to be used	
VO2 max (maximal oxygen consumption) on a treadmill; 15/10/02L. One-repetition maximum protocol; 16/10/07L.	
A3 Describe the research design to be used in your project	

3

Study Overview and Research Design:

All testing will be carried out within the exercise physiology laboratories at Cardiff Metropolitan University. This research requires all participants to attend the laboratory on three occasions. On the first visit, the participant will undergo a non-invasive vascular assessment and a maximal strength and fitness test. On the second visit, the participant's cardiovascular response to 1) a cold pressor test, 2) a static hand-grip, 3) a static leg press and 4) a supine cycling exercise will be assessed. On the final visit, the participant will undergo a volume challenge, during which succinylated gelatin (Gelofusine; 7ml/kg body weight) will be infused into an antecubital vein.
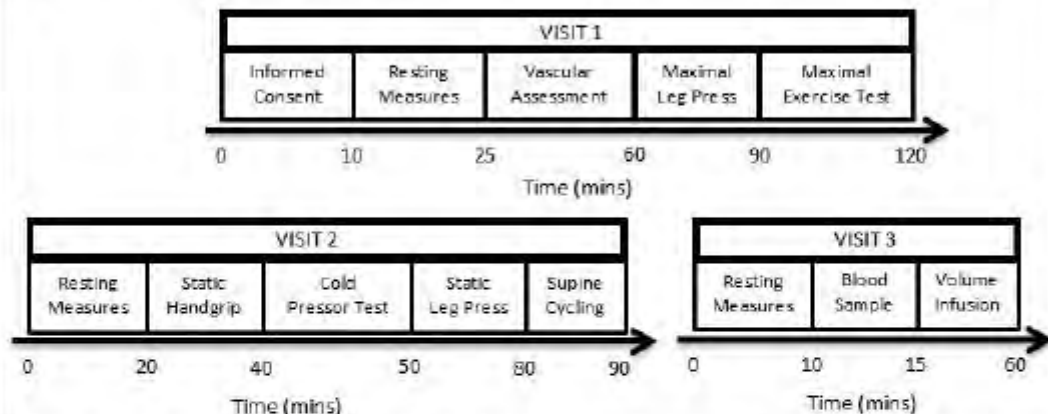
Following the first visit, the second and third visit will be separated by a minimum of one week and a maximum of three weeks. For all visits, the participants will be asked to attend the laboratory having abstained from strenuous exercise, alcohol and caffeine consumption for 24 hours. Additionally, for visit two and three, participants will attend having fasted for 6 hours prior to testing. All participants will attend the laboratory at a similar time of day, to control for individual diurnal variation in the parameters assessed. All data will be collected in a thermoneutral environment (~22°C).

Participant recruitment:

Four groups of participants (endurance athletes, resistance athletes, climbers and sedentary individuals; characteristics outlined below, see inclusion and exclusion criteria) will be recruited for this cross-sectional, repeated-measures study. We aim to recruit 10-15 male individuals aged 18-45 years in each group. To recruit individuals that are endurance trained, we will approach both the university and local, running/cycling/triathlon clubs. For resistance trained individuals, we will approach local gyms and for climbers, climbing centres. Recruitment for the sedentary males will be completed via poster advertisement (Appendix VII) around the University (both Cyncoed and Llandaff). In addition, emails and social media will be used to promote the research study. Interested individuals will be sent a participant information sheet (Appendix VI) and an ACSM pre-participation screening questionnaire (Appendix I) to return. All participants will be informed that Gelofusine is listed as a banned substance by UKADA and WADA as it can act as a potential masking agent/diuretic. Any interested athletes that are competing at

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an elite level, who may be subject to drug testing will be excluded from the Visit 3 assessment (see details below). The participants will then be contacted to discuss their involvement in the study.

Inclusion Criteria:
The specific inclusion criteria are detailed below;
- Male endurance athletes (>10 hours of training/week, for a minimum of two years)
- Male resistance athletes (>7 hours of training/week, for a minimum of two years)
- Highly trained male climbers (leading >French 6b, UIAA VII, for a minimum of two years)
- Sedentary males (<3 hours moderate intensity physical activity per week)

Exclusion Criteria:
All interested individuals, will first fill out the ACSM Pre-Participation Screening Questionnaire (Appendix I). Any individual that presents with three or more contraindications to exercise testing or meets any of the criteria below will be excluded from the study.
- Female (previous work has shown that haemodynamics are more variable in females due to the influence of natural, or prescribed, cycles in hormone levels. Given the nature of the study (repeated-measures design, with all visits needing to be conducted within three weeks of the first), it would be impossible to control for this variation in hormone levels).
- Smokers (cessation within 1 year).
- History of severe atopy (tendency to develop allergic diseases, e.g. allergic rhinitis and eczema).
- Asthma.
- A resting blood pressure over 140mmHg (systolic) or 90mmHg (diastolic).
- Currently taking prescribed medication for any cardiovascular risk factor.
- Previously instructed not to partake in any form of exercise by a doctor (general practitioner or hospital doctor).
- Any diagnosed or early family history of cardiovascular, autonomic or metabolic disease.
- Any use of illegal performance enhancing drugs.
- Any elite competitive performers who may be subject to random drug tests are not suitable for Gelofusine infusion and therefore will be excluded from the Visit 3 assessment.

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Visit 1
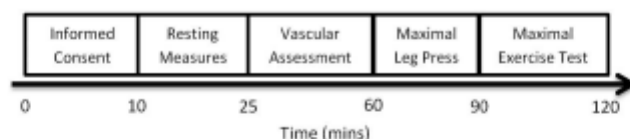
Informed Consent, Blood Pressure, Vascular Assessment and Maximal Testing (~ 120 minutes):
Following the completion of a physical activity readiness questionnaire (PAR-Q) (Appendix IV) and an informed consent form (Appendix III), stature (Holtain, Fixed Stadiometer, Pembs, UK) and body mass (SECA, Model 770, Vogel & Halke, Hamburg, Germany) will be measured. Anthropometric data will be collected through skinfold measurements (Baty International, Harpenden Skin Fold Calliper, Sussex, UK) at seven sites on the right side of the body in accordance with the ACSM guidelines[2]: chest, midaxillary, triceps, subscapular, abdominal, suprailiac and thigh. Duplicate measures will be taken at each site, and if the duplicate measurement is not within 2mm, a third measure will be taken.
Following 10 minutes of supine rest, blood pressure (manual sphygmomanometry) will be assessed.

Vascular Assessment (Pulse Wave Analysis (PWA) and Carotid-Femoral Pulse Wave Velocity (cf-PWV)):
The assessment of PWA and cf-PWV will be performed in accordance with the published guidelines[13], using the SphygmoCor system (SphygmoCor CVMS, AtCor Medical, Sydney, Australia). The arterial waveform is assessed using a high fidelity micromanometer tipped probe to obtain sequential ECG-gated pressure waveforms of the carotid and femoral artery, at the site of maximal arterial pulsation, which are analysed by the software package (SphygmoCor CVMS, AtCor Medical, Sydney, Australia).

Maximal Leg Press:
Immediately following this, participants will be required to perform a one-repetition maximum (1RM) double leg press. 1RM is defined as the maximum weight that can be lifted for one repetition. Participant's' 1RM for the double leg-press will be determined in accordance with the guidelines set by the National Strength and Conditioning Association. Following a warm-up set with a light resistance that will allow 5-10 repetitions, the participant will first attempt to lift 50% of their predicted 1RM, allowing for familiarisation with the correct lifting technique. After 2-3 minutes' rest, the load will be increased to be somewhat more difficult, based on the ease with which the previous trial was performed. This process will continue by increasing or decreasing the load until the participant can only complete one repetition using the proper lifting technique. The participant's' 1RM will be determined within 5 attempts. This protocol complies with current Cardiff Metropolitan University approved protocol (16/10/07L).

Maximal Exercise Test:
Following a minimum of 30 minutes and a maximum of one hour of rest (once haemodynamics return to baseline), participants will complete a maximal oxygen consumption test on a cycle ergometer (Lode Corival, Gronigen, The Netherlands). Due to the different fitness levels between the groups, each group will cycle at a different initial power output for the first minute; 50W at 60-80rpm for the sedentary group, 120W at 100-110rpm for endurance athletes and 80W at 80-100rpm for climbers and resistance athletes. Every 60 seconds following this, there will be an increase of power by 20W, until the

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participants reach a point of volitional exhaustion or signs of poor perfusion (cyanosis, dizziness) are observed. This protocol will comply with the current ACSM guidelines[4] and the current Cardiff Metropolitan University approved protocol (15/10/01L). During the test, oxygen consumption will be measured by a breath-by-breath analyser (Oxycon Pro, Jaeger, Hoechberg, Germany), whilst heart rate will be measured using a Polar heart rate monitor (Polar Electro, RS400, Kemple, Finland).

Visit 2

Resting Measures	Static Handgrip	Cold Pressor Test	Static Leg Press	Supine Cycling

0   20   40   50   80   90

Time (mins)

Protocol (~ 90 minutes):
Each test below will be separated by a monitored recovery period of at least 5 minutes, to ensure blood pressure and heart rate return to baseline prior to commencing the next test.

Resting Measures:
On arrival, participants will be asked to lie in the supine position on a tilt bed (at an angle of 45°) for 10 minutes and then resting measurements will be taken as described below:

Experimental measures to be taken at rest, during and following pressure challenges:
Central Hemodynamics:
Continuous beat-to-beat, non-invasive haemodynamics will be measured by attaching a blood pressure cuff to the participant's upper, non-dominant, arm and middle finger of the non-dominant hand (FinometerPro, FMS, Groningen, Netherlands). Analysis of blood pressure and heart rate data will be obtained in real-time using specialised data analysis software (LabChart Version 5.5.6, ADInstruments, Chalgrove, UK). In addition, manual brachial blood pressure readings will be taken with standard auscultation.

Blood vessel imaging:
Carotid strain and strain rate, diameter, wall thicknesses and blood flow velocity will be recorded at rest, during and immediately following pressure challenges. In addition, femoral and brachial artery diameter and velocities will also be recorded at rest. A 12-MHz multi-frequency linear array probe attached to a high-resolution ultrasound machine will be used to record these variables (Vivid q, GE Medical). All images will be taken by a trained sonographer.

Echocardiography
Echocardiographic images will be recorded with a 1.5 to 4-MHz phased array transducer on a commercially available ultrasound system (Vivid q; GE medical). Apical four-chamber views and parasternal short-axis views will be recorded at end-expiration to measure systolic (e.g. stroke volume,

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ejection fraction, longitudinal tissue velocities) and diastolic function (e.g. transmitral flow patterns). Images will be collected at rest, during and immediately following pressure challenges. All images will be taken by a sonographer who is highly trained in the field.

Static Handgrip:
Participants will then be asked to complete a maximal isometric contraction using a grip force transducer (MLT003/D Grip Force Transducer, ADInstruments, Chalgrove, UK) in preparation for a sustained isometric handgrip (IHG). All participants will be asked to complete the maximal effort in a supine position, using their left hand. To determine maximal force, participants will be asked to perform three separate maximal contractions separated by a short period of rest (approx. 1 minute).
Static handgrip exercise will be performed at 40% of maximum for 3 minutes. Central haemodynamics, blood vessel imaging and echocardiography measurements will be taken a minute before, continuously during, and for three minutes following the hand grip.

Cold Pressor Test (CPT):
All participants will be required to place their left hand into ice-cold (4°C) water for three minutes. Central haemodynamics, blood vessel imaging and echocardiography measurements will be taken (as described above) during a one minute baseline prior to the CPT, during the CPT, and during a three-minute recovery phase. This is a common protocol used in the assessment of autonomic function in young[3], old[4] and diseased[5] individuals and has been previously approved by the committee.

Static Leg Press:
Static leg press exercise will be performed at 20%, 40% and 60% of 1RM (derived from visit one). Participants will perform the leg press by extending their legs from a 90-degree bend (starting position), to a 60-degree leg bend, which they will hold for 2 minutes at each intensity, with 2 minutes' rest between each hold. Central haemodynamics, blood vessel imaging and echocardiography measurements will be taken (as described above) immediately before, continuously during and for two minutes following the final hold.

Supine Cycling:
Participants will be required to complete a 10-minute bout of supine cycling exercise (Lode, Angio 2003). Echocardiography measurements will be taken after three minutes of cycling at 50% estimated supine peak power. Seated cycling peak power will be calculated using the following equation[16] and deducted by 20% to reflect supine cycling peak power:

$$[(\text{height in cm} - \text{age in years}) \times (20 \text{ for men}) - 150 + (6 \times \text{weight in kg})] / 10$$

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Visit 3

Time (mins)
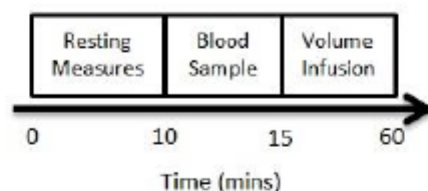
Protocol (~ 60 minutes):
Resting Measures:
On arrival, a highly-trained clinician will discuss the protocol with the participant, giving them the opportunity to ask any questions and ensure they fully understand the procedure and associated risks. They will then be asked to complete an additional informed consent form with the clinician present. Following this, participants will be asked to lie in the left lateral decubitus position for 10 minutes and then central haemodynamics, blood vessel imaging and echocardiography measurements will be taken (as described in visit two). The participants' legs will then be raised and resting measurements will be repeated.

Intravenous Gelofusine Infusion:
Once resting measures have been taken, the participant will remain lying down in the left lateral decubitus position whilst a highly-trained clinician inserts a small needle into an antecubital vein of their non-dominant arm. In line with guidelines (Appendix II and VIII), a venous blood sample will be taken and the participant's haematocrit and serum sodium concentration will be measured using an i-STAT device (Abbott, i-STAT1, Princeton, USA). If these values are outside the normal range (<40%[15] and <133mmol/l[15], respectively) then the participant will not undergo the infusion. Following this, 7ml/kg body weight of Gelofusine (succinylated gelatin 4%) will be infused intravenously over a 30-minute period. The initial 20-30ml will be administered slowly to monitor for any possible adverse reactions (should any reaction occur; the infusion will be stopped immediately and appropriate treatment will be given). Following this, the infusion rate will be specific to each individual, e.g. for a participant of 60kg, we will be infusing 420ml, whereas for a participant of 100kg, we will be infusing 700ml.
In accordance with the guidelines (Appendix II) a further measure of haematocrit will be taken half way through the infusion period; this will require the infusion to be stopped, allowing for a further blood sample to be taken before the infusion can resume. Another sample will also be taken post-infusion to monitor for any possible adverse reaction. All blood samples will be discarded immediately after use. Heart rate and blood pressure will be continuously monitored thoughout using the FinometerPro and manual brachial blood pressure will be taken every five minutes during the infusion. Pulse and oxygen saturation will also be continuously monitored throughout using a fingertip pulse oximeter (Choice Med, MD300C2, Beijing, China). Echocardiographic and blood vessel images will be taken half way through

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and twice post infusion (see Visit 2 for details); once in the left lateral decubitus position and again with legs raised. The participant will also undergo a brief clinical examination 20 minutes' post infusion, including a manual brachial blood pressure, jugular venous pressure assessment and a chest auscultation to monitor for any adverse effects.

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A4 Will the project involve deceptive or covert research?	No.
A5 If yes, give a rationale for the use of deceptive or covert research	
A6 Will the project have security sensitive implications?	No
A7 If yes, please explain what they are and the measures that are proposed to address them	

B PREVIOUS EXPERIENCE
B1 What previous experience of research involving human participants relevant to this project do you have?
Dr. Pugh has extensive experience of utilising the vascular and haemodynamic techniques outlined in this proposal both at rest and during exercise. Dr. Pugh has conducted numerous experimental studies to investigate the acute and chronic vascular adaptations to exercise and other physiological stimuli such as water immersion, heat exposure and lower body negative pressure[4-11]. Furthermore, Professor Shave has been researching the field of exercise and cardiovascular function for 20 years and has published >120 papers in the area. Importantly, the medical team have extensive experience of using volume expanders, such as Gelofusine, in clinical cohorts and so are well placed to oversee this aspect of the study.

B2 Student project only
    What previous experience of research involving human participants relevant to this project does your
    supervisor have?

C POTENTIAL RISKS
C1 What potential risks do you foresee?
a.   Maximal Exercise Test: The maximal exercise test may be uncomfortable for individuals unaccustomed to exercise. There is a minimal risk of dizziness and fainting caused by a maximal exercise effort. Following the exercise test, subjects may experience muscle soreness, which will disappear within a few days. b.   Volume Infusion: Although minimal, there is a potential risk of bruising and discomfort with insertion of the needle. There is also a small risk of infection of the area where the needle is inserted. Other adverse risks include allergic skin reactions and a mild increase in body temperature. Furthermore, there is a very minor risk of an anaphylactoid reaction to Gelofusine; symptoms of which include mild influenza-like symptoms, tachycardia, respiratory difficulties, hypotension and dizziness. However, the risks of these occurring are minimal and numerous infusions have been performed successfully and safely in healthy and diseased participants[13,14] (see Appendix V for full risk assessment). c.   Cold Pressor Test: The participant may experience some slight discomfort when their dominant hand is placed in cold water.
C2 How will you deal with the potential risks?
a.   Maximal exercise test: As the health status of all participants will be assessed via the ACSM pre-participation questionnaire, the risk of exercise-induced complications will be minimal. The risk of dizziness and fainting following maximal exercise effort will be further minimised by performing a cool down immediately following maximal effort, which will be achieved by reducing the exercise workload to <50% of maximum ability and encouraging the participant to perform exercise at these light intensities for 3-5 minutes following the preceding maximal effort.

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b.   Volume Infusion: The volume infusion will be overseen by a highly-trained clinician from the University Hospital of Wales (who has extensive experience of using this plasma expander) and has provided a letter of support stating that our protocol is in accordance with theirs (Appendix IX). The site of insertion will be cleaned with an alcohol swab beforehand and the clinician will wear appropriate protective gloves whilst inserting the catheter to ameliorate the risk of infection. Additionally, all equipment will be appropriately sterilised and once infusion is complete, all equipment will be suitably discarded in keeping with BASES laboratory guidelines. Furthermore, the initial 20-30 mL of the infusion will be administered slowly to monitor for adverse reactions. Should an adverse reaction occur (the participant will be continuously monitored for early signs of anaphylaxis, e.g. rash, wheeze, hypotension), then the infusion will be stopped immediately and appropriate treatment will be given until symptoms have resolved (clinicians will have access to resuscitation equipment, including adrenaline). Participant's haemodynamics (blood pressure and heart rate), pulse and oxygen saturation will be monitored continuously throughout and post-drug administration. In addition, the participant will undergo a brief clinical examination post infusion before leaving the laboratory.

c.   Cold Pressor Test: Participants will be able to withdraw their hand from the iced water at any time if they feel too uncomfortable.

A comprehensive risk assessment has been conducted for all procedures involved in this protocol (see Appendix V).

When submitting your application you MUST attach a copy of the following:
- All information sheets
- Consent/assent form(s)

An exemplar information sheet and participant consent form are available from the Research section of the Cardiff Met website.

References

1. Atkinson, G., Batterham, A.M., Kario, K., Taylor, C.E., Jones, H. (2014) Blood pressure regulation VII. The "morning surge" in blood pressure: measurement issues and clinical significance. *Eur J Appl Physiol*; 114(3):521-9.
2. Pescatello, L.S. (2014) ACSM. ACSM's Guidelines for Exercise Testing and Prescription. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health.
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4. Okada, Y., Jarvis, S.S., Best, S.A., Edwards, J.G., Hendrix, J.M., Adams-Huet, B., *et al.* (2016). Sympathetic Neural and Hemodynamic Responses During Cold Pressor Test in Elderly Blacks and Whites. *Hypertension*; 67(5):951-8.
5. Westheim, A., Os, I., Thaulow, E., Kjeldsen, S.E., Eritsland, J., Eide, I.K. (1992). Haemodynamic and neurohumoral effects of cold pressor test in severe heart failure. *Clin Physiol*; 12(1):95-106.
6. Pugh, C.J.A., Sprung, V.S., Green, D.J., Cable, T.N, Jones, H., Cuthbertson, D.J., Kemp, G.J., Richardson, P., Shojaee-Moradie, F. and Umpleby, M.A. (2014a). Exercise training reverses endothelial dysfunction in nonalcoholic fatty liver disease. *American Journal of Physiology - Heart and Circulatory Physiology*; 307(9): H1298-H1306.

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9. Carter, H.H., Spence, A.L., Pugh, C.J.A., Ainslie, P.H., Naylor, L.H., Green, D.J. (2014). Cardiovascular responses to water immersion in humans: Impact on cerebral perfusion. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology;* 306: R636–R640.

10. Carter, H.H., Spence, A.L., Atkinson, C.L., Pugh, C.J.A., Naylor, L.H., Green, D.J. (2013). Repeated core temperature elevation induces conduit artery adaptation in humans. *European Journal of Applied Physiology;* 114(4): 859-65.

11. Thijssen, D.H.J., Atkinson, C.L., Ono, K., Sprung, V.S., Spence, A.L., Pugh, C.J.A., Green, D.J. (2014). Sympathetic nervous system activation, arterial shear rate and flow mediated dilation. *Journal of Applied Physiology;* 116:1300-1307.

12. Lobo, D.N., Aloysius, M.M., Wicks, C., Nunes, Q.M., Allison, S.P., Stanga, Z., Ingram, K. L. and Risch, L. (2010) Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: A randomized, three-way crossover study in healthy volunteers. *Critical Care Medicine;* 38:464-470.

13. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, *et al.* (2012). Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *Journal of Hypertension;* 30(3):445-8.

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15. In accordance with University Hospital of Wales guidelines, as advised by study clinician, Dr Zaheer Yousef.

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Chapter 4

ORIGINAL ARTICLE

Right Ventricular Function and Region-Specific Adaptation in Athletes Engaged in High-Dynamic Sports

A Meta-Analysis

BACKGROUND: Structural remodeling of the right ventricle (RV) is widely documented in athletes. However, functional adaptation, including RV pressure generation and systolic free-wall longitudinal mechanics, remains equivocal. This meta-analysis compared RV pressure and function in athletes and controls.

METHODS: A systematic review of online databases was conducted up to June 4, 2020. Meta-analyses were performed on RV systolic pressures, at rest and during exercise, tricuspid annular plane systolic displacement, myocardial velocity (S'), and global and regional longitudinal strain. Bias was assessed using Egger regression for asymmetry. Data were analyzed using random-effects models with weighted mean difference and 95% CI.

RESULTS: Fifty-three studies were eligible for inclusion. RV systolic pressure was obtained from 21 studies at rest ($n=1043:1651$; controls:athletes) and 8 studies during exercise ($n=240:495$) and was significantly greater in athletes at rest (weighted mean difference, 2.9 mmHg [CI, 1.3–4.5 mmHg]; $P=0.0005$) and during exercise (11.0 [6.5–15.6 mmHg]; $P<0.0001$) versus controls. Resting tricuspid annular plane systolic displacement ($P<0.0001$) and S' ($P=0.001$) were greater in athletes. In contrast, athletes had similar RV free-wall longitudinal strain (17 studies; $n=450:605$), compared with controls but showed greater longitudinal apical strain (16 studies; $n=455:669$; 0.9%, 0.1%–1.8%; $P=0.03$) and lower basal strain (−2.5% [−1.4 to −3.5%]; $P<0.0001$).

CONCLUSIONS: Functional RV adaptation, characterized by increased tricuspid annular displacement and velocity and a greater base-to-apex strain gradient, is a normal feature of the athlete's heart, together with a slightly elevated RV systolic pressure. These findings contribute to our understanding of RV in athletes and highlight the importance of considering RV function in combination with structure in the clinical interpretation of the athlete's heart.

Tony G. Dawkins, MPhil
Bryony A. Curry, MPhil
Stephen P. Wright, PhD
Victoria L. Meah, PhD
Zaheer Yousef, MD
Neil D. Eves, PhD
Rob E. Shave, PhD
Michael Stembridge, PhD

CLINICAL PERSPECTIVE

What Is New?

Global and regional structural remodeling of the athlete's right ventricle (RV) is well characterized, yet functional adaptation of the RV remains unclear. This meta-analysis provides evidence of an elevated RV systolic pressure in athletes both at rest and during exercise, which is proportional to cardiac output. RV systolic myocardial displacement and velocity are greater in athletes compared with controls, and longitudinal deformation is lower at the base of the RV but greater at the apex in athletes. Therefore, consistent with structural remodelling, functional adaptation is region-specific, affecting the base and the apex of the RV differentially.

What Are the Clinical Implications?

Differentiation of training-induced RV physiology from pathology is problematic for the clinician, when based upon structure alone. Differences in myocardial function can support clinical decision-making and help to identify abnormal RV morphology. Clinicians working with athletes can expect to see RV enlargement and elevated right ventricular systolic pressures (≈ 40 mm Hg) and should be aware of regional differences in function. Tricuspid annular displacement and velocity may be elevated. Furthermore, lower basal longitudinal strain and an augmented base-to-apex strain gradient may be considered a normal feature of the athlete's heart.

Structural remodeling of the right ventricle (RV) in response to exercise-training, including increased end-diastolic volume, basal dilatation, and a highly trabeculated apex, has been widely evidenced in endurance athletes[1-3] and is used to differentiate pathology in sports cardiology.[4] However, functional adaptation of the RV is less clear. At rest, RV wall stress is low, corresponding with low pressures in the pulmonary circuit. During exercise, however, RV systolic pressure (RVSP) increases to drive stroke volume (SV) in the face of higher downstream pulmonary artery systolic pressure, secondary to high circulatory flow.[5] In addition to the high RV load experienced during exercise, athletes may also be exposed to an elevated hemodynamic load, owing to an expanded blood volume[6] and an increased RVSP at rest[7,8]; although the latter has not been consistently reported.[5,9-11] As such, systolic RV function in athletes may be altered by hemodynamic loading conditions,

intrinsic myocardial adaptation, and/or structural remodeling. RV contraction is predominantly driven by longitudinal shortening of the RV free-wall and interventricular septum, with contribution from circumferential muscle fiber constriction and late infundibular contraction.[12,13] Yet, consistent with structural remodelling,[14,15] functional adaptation may be region-specific, affecting the base and the apex of the RV differentially. Consequently, the aims of this meta-analysis were to investigate the influence of long-term exercise training on (1) RVSP at rest and during exercise and (2) RV free-wall and regional systolic functional adaptation. To address these aims, we compared RVSP, tricuspid annular displacement and velocity, and RV free-wall deformation between athletes and controls.

METHODS

Protocol

The authors declare that all supporting data are available within this article and its Data Supplement. This meta-analysis was registered a priori with PROSPERO (REGISTRATION: URL: https://www.clinicaltrials.gov; Unique Identifier: CRD42020206091) and conducted in accordance with PRISMA guidelines.[16] Ethical approval was granted by the Cardiff School of Sport and Health Sciences Research Ethics Committee (PGR-3419).

Search Strategy and Inclusion Criteria

The participants, interventions, comparisons, outcomes, and study design framework guided this study.

Participants

The population of interest were highly trained athletes (aged ≥18 years) from sports with a high-dynamic component, as defined by the Mitchell criteria (ie, regular contraction of large muscle groups and sustained increase in oxygen consumption).[17]

Intervention

No intervention was required.

Comparison

The comparator was a nonathletic control group (aged ≥18 years), without history or evidence of current or chronic cardiovascular, respiratory or metabolic disease.

Outcome Variables

Primary outcome variables included RVSP obtained by noninvasive echocardiography or invasively by right-heart catheterization, (1) at rest and (2) in response to dynamic exercise matched to an absolute or relative exercise intensity between groups. Other measures of RV systolic function obtained at rest included tricuspid annular plane systolic excursion (TAPSE), systolic myocardial velocities (S'), and free-wall and regional (base and apex) longitudinal strain and strain rate;

obtained via echocardiography or cardiac magnetic resonance imaging. RV free-wall strain was taken as the arithmetic mean of the 3 segments of the RV free-wall. RV chamber dimensions and areas were also extracted.

Study Designs

Original publications written in English were included. Reviews, editorials, case reports, and unpublished data were excluded. Studies of longitudinal design were eligible to be included, providing the training intervention was >2 years in duration and the weekly training volume >6 hours/week.

Information Sources

A comprehensive search of peer-reviewed studies published before June 4, 2020 that examined RVSP and RV systolic function was conducted. Specifically, publicly available databases (PubMed, MEDLINE, Scopus, Science Direct and Web of Science) were searched using the following search string: "Right ventric* OR pulmonary arter* OR pulmonary pressure AND function* OR strain OR mechanics OR adaptation OR remodel* OR response OR exercise OR deformation* AND athlete OR endurance." Reference lists from included articles were also examined in to identify any additional relevant studies. Authors were contacted for data and methodological clarification where necessary.

Study Review and Data Extraction

Titles and abstracts of identified publications were screened using an online reviewing software (Covidence, Veritas Health Innovation, Ltd, Australia). Full text articles were retrieved for relevant studies and were independently assessed for eligibility against participants, interventions, comparisons, outcomes, and study design inclusion criteria by 2 reviewers (T.G.D. and B.A.C.).

Age, sex, training status, and training mode of participants were recorded, and measures of RVSP and RV function were extracted. Studies were subcategorized as males (M) and females (F). Where there were multiple athletic subgroups but only one control population, data were extracted only from the athletic group performing the greatest volume (hours) of dynamic exercise. If relevant data were included in graphical format, numerical data were retrieved using an open-source software program (WebPlotDigitizer, version 4.3). Data presented as median and range were transformed to mean and SD.[18] Data presented as mean and CI were transformed to mean and SD using the following formula: $SD=\sqrt{nx}$ (Upper limit of CI–Lower limit of CI)/3.92.

Statistical Analyses

Meta-analyses were computed using the DerSimonian and Laird method[19] and applied to all continuous primary variables to determine the weighted mean difference (WMD) and 95% CI between control participants and athletes. WMD corresponding to a small Cohen's d effect size (0.2) were considered the minimum clinically important difference.[20] The pooled estimate for the lower and upper reference value (mean value±2 SD's) were calculated, with 95% CI for further robustness (available in Table V in the Data Supplement). A

random-effects model was selected, a priori, reflecting the anticipated heterogeneity of the data, owing to the potential variety of sporting disciplines, athletic training status (ie, training type, volume, intensity, and load) and methodological differences in data acquisition. Between-study heterogeneity was evaluated using χ^2 with a $P<0.05$ indicating significant heterogeneity, and the percentage of variability in the effect estimates because of heterogeneity evaluated using the inconsistency index (I^2).[21] Publication bias was assessed using funnel plots and the Egger regression method, with a $P<0.1$ considered significant.[22] Forest plots were created using Review Manager (RevMan [Computer program] Version 5.4) and presented as compiled figures. Random effects meta-regressions for age, sex, and training hours were conducted for each parameter using the metareg command in Stata (Version 16). RVSP/cardiac output slopes (ie, increase in RVSP per unit increase in cardiac output) were calculated at baseline and during exercise. Grouped mean slopes were compared using an independent samples t test (Graphpad Prism, version 8.4.2; GraphPad Software Inc, San Diego, CA).

RESULTS

Study Selection

Figure 1 provides a summary of the study selection, included studies and number of participants for each outcome variable. From the 1974 studies identified in the initial search, 53 studies involving 2908 athletes and 2614 controls were included in the final analyses of all variables. Two studies reporting RVSP were excluded due to duplication of study data, which was clarified via correspondence with the authors.[5,23] Three studies reported athletic and control datasets for both males and females.[24–26] RVSP was assessed via echocardiographic assessment of tricuspid regurgitant velocity in 20 of 21 included studies. One study collected RVSP invasively via balloon tipped catheter.[27] Further details of individual studies are included in Table I in the Data Supplement.

Right Ventricular Systolic Pressure

The total number of studies included for each primary outcome variable differs and is highlighted in Figure 1. In agreement with previous analyses, RV dimensions were consistently greater in athletes compared with controls (Table II in the Data Supplement). Normative reference ranges obtained for each parameter are provided in Table V in the Data Supplement. Meta-analysis of RVSP at rest, and in response to exercise, revealed a WMD between the athletes and controls of 2.9 mm Hg (95% CI, 1.3–4.5 mm Hg) and 11.0 mm Hg (95% CI, 6.5–s15.6 mm Hg), respectively (Figure 2, Table III in the Data Supplement). Statistical heterogeneity was observed both at rest (χ^2, 306, $P<0.0001$; I^2 value of 93%) and during exercise (χ^2, 34, $P<0.0001$; I^2 value of 79%). There was evidence of publication bias for RVSP both at rest (Egger test, 2.85, $P=0.013$) and during exercise (Egger test, 2.69, $P=0.036$).
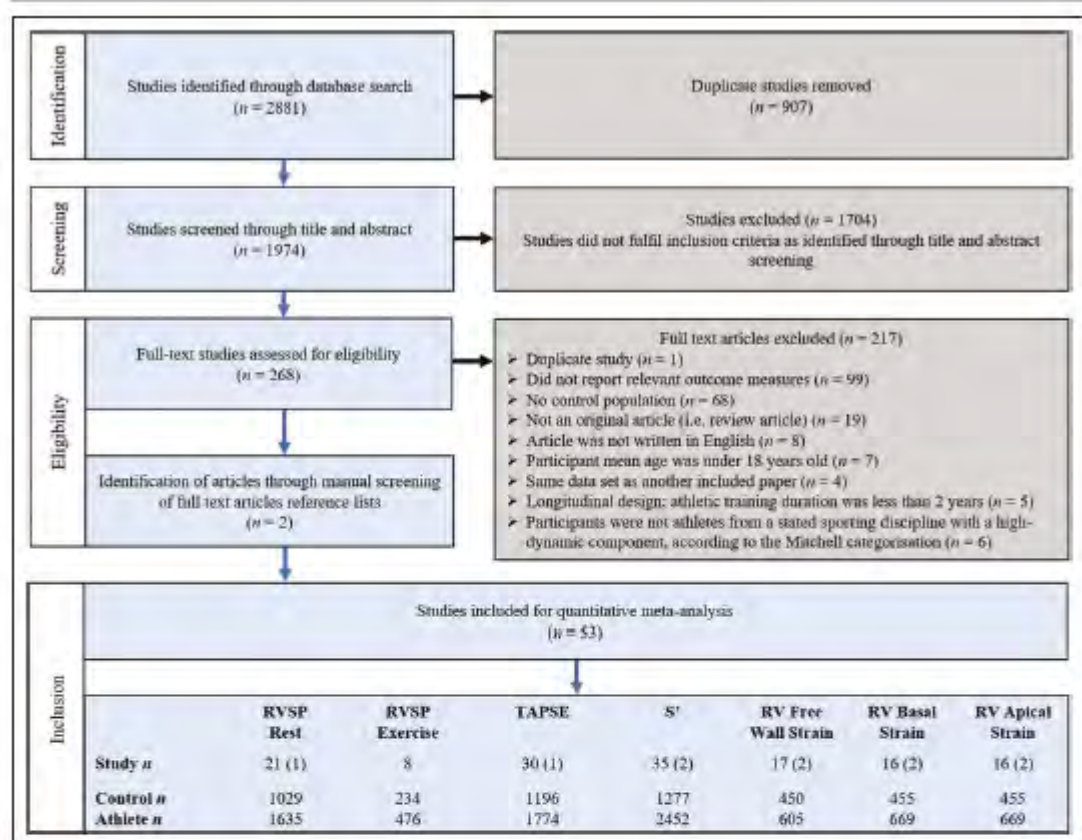
Figure 1. Flow diagram showing study inclusion and exclusion processes.
Brackets after study n indicate where studies have been split into substudies, where sex has been explicitly differentiated. RV indicates right ventricular; RVSP, right ventricular systolic pressure; S', systolic myocardial velocity; and TAPSE, tricuspid annular plane systolic excursion.

From rest to exercise, there was no significant difference in the slope of mean RVSP increase per unit increase in mean cardiac output between groups (Figure 3).

Right Ventricular Systolic Function

TAPSE and S' were greater in athletes than in controls (Tables 1 and 2; Figures I and II in the Data Supplement). RV global (6-segment) and free-wall (3-segment) longitudinal strain were not different between athletes and controls. However, regional strain at the apex was greater (more negative) in athletes (WMD, 0.9% [95% CI, 0.1%–1.8%]) but lower at the base in athletes compared with controls (WMD, −2.5% [95% CI, −1.4% to −3.5%], Figure 4; Table IV in the Data Supplement). For all primary outcome variables, there was significant evidence of high study-to-study heterogeneity, but no statistical evidence of publication bias (Figure 4).

RV free-wall strain rate was lower in athletes compared with controls (WMD −0.13/second, $P=0.0001$, Tables 1 and 2; Figure III in the Data Supplement). Strain

rate in athletes was also at the base of the RV (WMD, −0.26/second, $P=0.01$), but not at the apex (WMD, −0.02/second, $P=0.60$).

Meta-Regression

Sex was identified as an important determinant of variation in RV S', with the WMD between athletes and controls being lower in females compared with males. The effects of age, sex, and training hours were not significant determinants of variation for any other RV parameter (Table VI in the Data Supplement). However, because of insufficient data availability, it should not be misconstrued that these factors do not influence these RV measures.
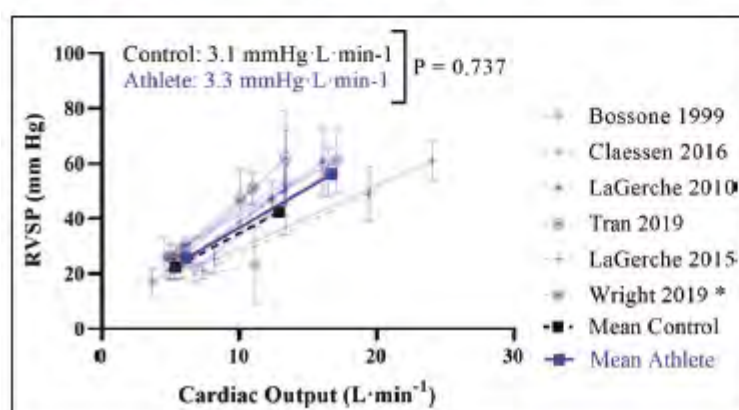
DISCUSSION

Our meta-analysis of studies reporting RVSP and systolic function indicates that, in comparison to controls, (1) athletes demonstrate an elevated resting RVSP, which is further increased (compared with controls) during

Figure 2. Individual forest plots showing weighted mean difference (WMD), 95% CIs, effect size (Cohen's d), and minimum clinically important difference (MCID) for studies included in meta-analysis of right ventricular systolic pressure (RVSP) at rest (21 studies, Control n=1029; athlete n=1635) and during exercise (8 studies, control n=234; athlete n=476).
The mean age across studies was 31 y for both athletes and control populations. ‡Numerical data were retrieved from graphical format. *Pressure measurements were obtained via invasive balloon catheter. All other studies used transthoracic echocardiography to estimate RVSP from the tricuspid regurgitant velocity. NA indicates not applicable since exercise was not performed in this study; and RAP, right atrial pressure.

exercise; (2) measures of RV systolic function, including tricuspid annular displacement and velocity (TAPSE and S'), are greater in athletes. However, (3) athletes demonstrate a similar global and free-wall longitudinal strain, but (4) it is achieved with greater longitudinal strain at the apex and lower strain and strain rate at the base of the RV (Figure 5). This meta-analysis provides evidence of region-specific RV adaptation in athletes, which has important implications for future interpretation of physiological and pathological remodeling of the RV.

Dynamic Exercise Training Is Associated With Elevated RV Pressure, Both at Rest and During Exercise

RV ejection of blood and pulmonary artery systolic pressure are tightly coupled. As such, it is recognized that

a greater SV and pulsatile blood flow increases pulmonary artery systolic pressure and upstream RVSP.[78] However, because of the compliance characteristics of the pulmonary vasculature, the SV contribution to systolic pressure is moderate.[29] Nonetheless, this meta-analysis provides evidence of a consistent elevation in resting RVSP in athletes. As such, athletes may be exposed to elevated RV loading conditions at rest, although the magnitude of the higher pressure is relatively mild. It should be recognized that our analyses highlighted the potential of bias in both resting and exercise RVSP measures. While there are numerous sources of bias, which may influence these results, including publication bias,[22] it is noteworthy that the largest trials that were also blinded for analysis showed significant elevations in RVSP in athletes.[7] Exercise stresses the pulmonary vasculature because of an increase in cardiac output,

Figure 3. Mean right ventricular systolic pressure (RVSP) and cardiac output values for each study are presented where possible (error bars represent 95% CI), with slopes intersecting mean baseline and exercise data.
Grouped mean slopes are represented by dashed black lines for nonathletic controls and solid blue lines for athletes. *Pressure measurements were obtained via invasive balloon catheter. All other studies used transthoracic echocardiography to estimate RVSP from the tricuspid regurgitant velocity.

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Table 1. Meta-Analysis Results for Displacement and Velocity Parameters of Right Ventricular Systolic Function and Strain Rate Measures in Athletes and Nonathletic Controls

Parameter	Studies (n)	Controls (n)	Athletes (n)	MCID (0.2×SD$_{pooled}$)	WMD (95% CI)	Effect size (Cohen's d)	P value	I²	Eggers test (P value)
TAPSE, mm	30	1196	1774	0.7	−1.8 (−1.0 to −2.5)	0.4	<0.0001	86	0.244
RV S', cm/s	35	1277	2452	0.4	−0.7 (−0.3 to −1.1)	0.4	0.001	87	0.452
RV strain rate									
RV free-wall strain rate (s⁻¹)	5	116	149	0.04	−0.13 (−0.08 to −0.19)	0.6	0.0001	0	0.408
RV basal strain rate (s⁻¹)	5	150	287	0.06	−0.26 (−0.06 to −0.46)	0.8	0.01	90	0.678
RV apical strain rate (s⁻¹)	5	150	287	0.05	−0.02 (0.05 to −0.09)	−0.0	0.57	25	0.311

MCID indicates minimum clinically important difference; RV, right ventricle; S', systolic myocardial velocity; TAPSE, tricuspid annular plane systolic excursion; and WMD, weighted mean difference.

SV and left atrial pressures.[30] Pulmonary vascular resistance decreases during exercise in healthy individuals because of a compensatory increase in cross-sectional area via distention and recruitment of pulmonary vessels.[31] However, since resistance is already low at rest, there is limited capacity to adequately mitigate rising pulmonary artery load. Previous studies have demonstrated the considerable pressure generating capacity of the RV,[27] which results in a disproportionately greater increase in RV wall stress, in comparison to the LV.[5] In our meta-analysis, RVSP in athletes during moderate-to-intense exercise was consistently elevated beyond that of controls. However, the relationship between increases in RVSP and cardiac output were similar in both athletes and nonathletes, as shown in Figure 3. This finding indicates that RVSP is not altered by training when cardiac output is controlled for, as previously evidenced.[32] However, the greater capacity to increase cardiac output among athletes is therefore associated with greater RVSP. As such, exercise training involving

Table 2. Normative Reference Values for RV Pressure and Function

Variable		Lower reference value	Mean	Upper reference value
RVSP rest, mm Hg	Control	13.3	21.8	30.3
	Athlete	13.9	24.7	35.5
TAPSE, mm	Control	16.9	23.5	30.1
	Athlete	17.5	25.2	32.9
RV S', cm/s⁻¹	Control	8.8	12.9	16.9
	Athlete	9.2	13.6	18.1
RV free-wall strain, %	Control	−20.7	−26.8	−32.8
	Athlete	−20.1	−26.4	−32.6
RV basal strain, %	Control	−17.4	−25.3	−33.2
	Athlete	−15.3	−22.9	−30.4
RV apical strain, %	Control	−20.1	−28.4	−36.7
	Athlete	−21.2	−29.3	−37.5

95% CIs for mean, lower and upper reference values are provided in Table V in the Data Supplement. RV indicates right ventricle; RVSP, right ventricular systolic pressure; S', systolic myocardial velocity; and TAPSE, tricuspid annular plane systolic excursion.
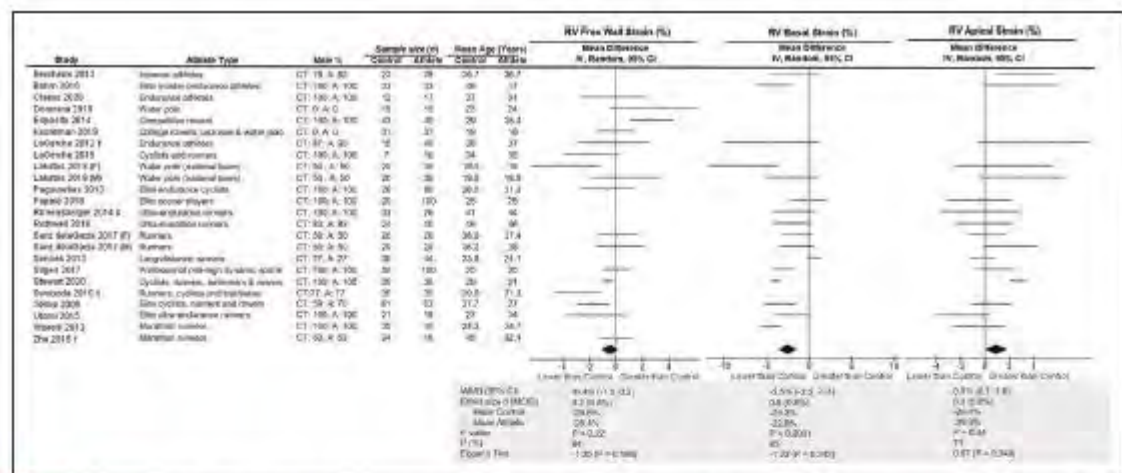
high cardiac output is associated with both elevated volume and pressure loading conditions for the RV, at rest and during exercise.

Enhanced Right Ventricular Function in Athletes, Assessed Via Displacement and Velocity

Structural RV remodeling is well established in endurance athletes. Several reviews have highlighted the frequent observation of ventricular enlargement, dilatation of the ventricular cavity, and outflow tract among athletes,[1,33] which is further supported by the findings of this meta-analysis (Table II in the Data Supplement). Region-specific structural adaptation has also been reported, including a bulging of the basal free-wall,[34] apical displacement,[35] and apical hypertrabeculation.[3] Relatively fewer investigations, in contrast, have specifically studied the functional adaptation of the athlete's RV. To fully understand the extent of RV remodeling, it is important that functional adaptation is also considered alongside structural remodeling.

The present meta-analysis provides evidence of a greater basal myocardial longitudinal displacement (TAPSE) at a faster rate (S') in athletes compared with nonathletic controls. These findings, however, may reflect the size and load dependence of these measures of systolic function,[36] and such observations in athletes may be considered epi-phenomena, secondary to structural remodeling and preload status.

Deformation of the Right Ventricle and Region-Specific Remodeling in Athletes

In contrast to displacement and velocity indices of RV systolic function, strain analysis permits the assessment of regional deformation. We observed no difference in 6-segment global longitudinal strain, or 3-segment free-wall longitudinal strain (ie, inclusion or exclusion of the septum, respectively) between athletes and controls. Unlike myocardial velocities, RV strain measures are relatively more size independent,[2] which may partly explain

Figure 4. Individual forest plots showing weighted mean difference (WMD), 95% CIs, effect size (Cohen's d) and minimum clinically important difference (MCID) for studies included in the meta-analysis of right ventricular (RV) free-wall (17 studies, Control n=450; athlete n=605) and region-specific strain (16 studies, Control n=455; athlete n= 669).
†Strain values were obtained via magnetic resonance imaging. All other studies utilized speckle tracking echocardiography. ‡Numerical data were retrieved from graphical format. Studies differentiating sex were divided into females (F) and males (M).

the inconsistency between displacement and velocity measurements and deformation-based indices of RV function. Nevertheless, the present meta-analysis provides evidence of a lower RV basal strain in athletes, but a greater reliance on apical strain and therefore greater base-to-apex strain gradient, in comparison to controls.

While comparatively fewer studies collected strain rate data, we also report consistent evidence of lower free-wall and basal RV strain rate. As there is tight coupling between RV elastance (contractility) and pulmonary arterial elastance (effective arterial load) throughout a range of physiological settings,[37,38] it has been suggested that
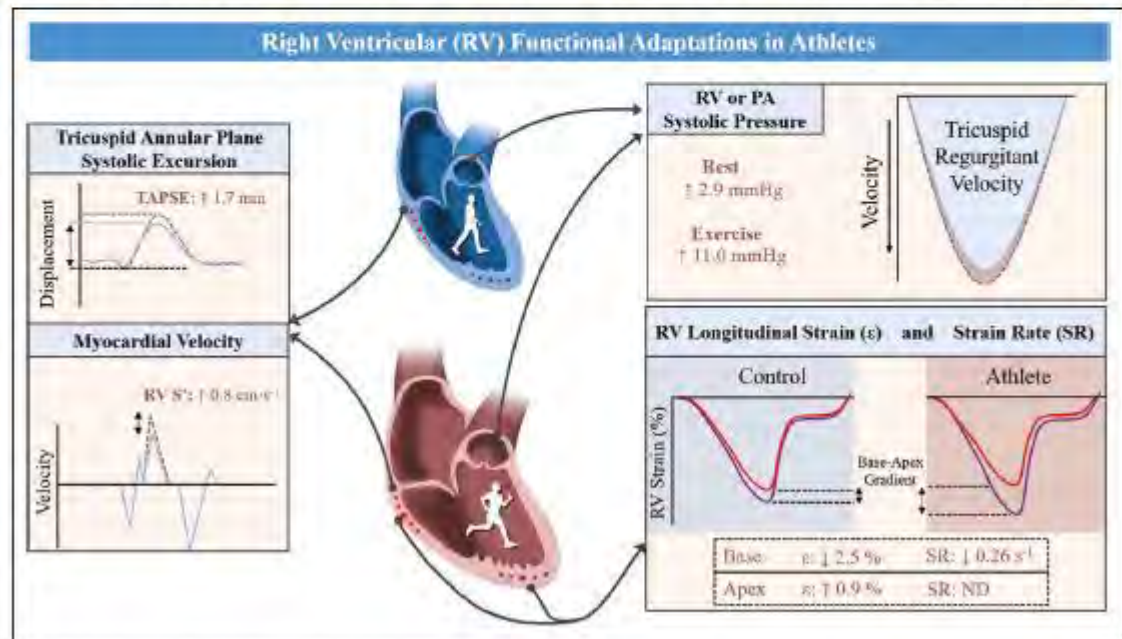
Figure 5. Right ventricular (RV) functional adaptations in endurance athletes.
Values presented are weighted mean difference (WMD) between nonathletic controls and athletes and visually depicted with dashed brown lines. Primary findings include a greater tricuspid annular displacement and myocardial velocity, and region-specific remodeling of the RV free-wall, involving a lower strain and strain rate at the base and a greater strain at the apex, in comparison to nonathletic controls. ND indicates no significant difference; PA, pulmonary artery; S', right ventricular systolic myocardial velocity; SR, strain rate; and TAPSE, tricuspid annular plane systolic excursion.

lower RV contractility at rest in athletes may reflect a maintenance of ventricular-arterial coupling, by matching contractility to low afterload.[15] Arterial elastance (calculated as RVSP/SV) may be expected to be lower in athletes in whom SV is far greater but RVSP is only moderately raised. Furthermore, as the basal section contributes most to overall RV volume, less deformation of this segment is required to eject the same volume,[14,15] relative to the apex. The mechanisms resulting in training-induced alterations in region-specific function, however, are poorly understood, but likely include structural remodeling and/or architectural fiber alignment, altered loading conditions, or intrinsic myocardial cellular and molecular adaptation.[39,40] It is possible that these region-specific findings reflect an increased reserve capacity that can be used in situations of high demand, such as exercise, similar to that which has been postulated for the observed reduction in left ventricular torsion in athletes.[41] Indeed, La Gerche et al[15] demonstrated an enhanced contractile reserve of the RV basal segment upon exercise. Few studies have assessed RV wall deformation in athletes during exercise[9,15,26]; however, characterization of the RV response to hemodynamic perturbation is crucial to further our understanding the athlete's RV.

Clinical Implications

Differentiating training-induced physiological RV adaptations from pathological RV myopathy is clinically important in the care of athletes. RV enlargement is frequently observed in athletes from high-dynamic sporting backgrounds, for which upper reference limits have been identified.[42] In addition to RV enlargement, we demonstrate altered resting function in athletes, which is dependent on the variable assessed (ie, myocardial displacement, velocity, or deformation) and the region of the RV that is examined. Our data support the implementation of a higher upper reference value for TAPSE (33 mm) beyond that previously recommended in athletes[42]; however, the upper reference value for RV S' is within the upper limits of normal for the general adult population.[43] Furthermore, a slightly lower basal longitudinal strain, and an enhanced base-apex strain gradient may be considered normal functional features of the athlete's heart. Notwithstanding, a severe reduction in basal strain (lower reference value <15%) or a lower functional myocardial reserve during stress testing may warrant further clinical consideration.[9] Finally, the upper reference value for RVSP in athletes was 36 mm Hg; however, 7/21 studies did not consider the influence of right atrial pressure together with the trans-tricuspid pressure gradient. As such, the results from this meta-analysis support the previously recommended upper limit of 40 mm Hg for RVSP at rest in athletes.[7] In summary, clinicians working with athletes can expect RV enlargement and elevated pulmonary pressure and should be aware of potential differences in regional function, characterized by a more dynamic apex, a modestly reduced basal longitudinal strain and an augmented base-apex strain gradient. It is important to note, however, that overlap will exist between athletic remodeling and certain pathologies, such as arrhythmogenic cardiomyopathy. Therefore, clinical investigation should utilize a multiparametric approach to assist with diagnostic evaluation.

Limitations and Future Research

While the present meta-analysis offers insight into the region-specific functional adaptation of the athlete's heart, limitations of this study must be acknowledged. We included studies that assessed both males and females within this analysis; however, physiological differences between sexes may have influenced our findings. For example, RV strain is consistently elevated in females across all segments.[44] Further study is therefore required to identify the specific influence of sex on training-induced functional remodeling of the RV; it is possible that, as with structural remodeling of the LV,[45] functional adaptation associated with dynamic exercise is diminished in females. While meta-regression did not identify sex as a determinant of variability for RV parameters, male dominated studies largely outweighed female studies. Additionally, we acknowledge that remodeling is dependent upon volume, intensity, and the type of exercise training. While the current study employed a range of sports involving different exercise doses, we categorized sports based on a predetermined criteria that is routinely used in sports cardiology, based on the hemodynamic profile of the activity.[17] Rigorous characterization of RV function in strength-trained athletes, however, remains an important area of future work. Future studies should assess whether regional measures of RV function regress following a period of detraining, as occurs with RV structure.[46] The high degree of heterogeneity across studies for all parameters should be considered when interpreting the results of this study. Furthermore, we cannot neglect the risk of publication bias, inherent with all meta-analyses, despite statistical interrogation. Finally, while meta-analyses are useful in defining population central tendency data, in clinical practice, it is the outliers that represent the challenge and knowledge of the normal population does not preclude the need for detailed follow-up in these individuals.

Conclusions

This meta-analysis, based on observational data, shows that athletes may be expected to generate a greater RVSP, both at rest and during exercise; however, this relationship appears to be proportional to cardiac output. Furthermore, RV systolic myocardial displacement and velocity at the tricuspid annulus is greater in athletes,

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in comparison to controls, despite lower myocardial deformation at the base of the RV free-wall and elevated apical deformation. Thus, region-specific adaptations of the RV free-wall, characterized by a widening of the base-to-apex strain gradient, may be considered a normal feature of the athlete's heart. These findings contribute to our understanding of RV remodeling in athletes and highlight the importance of considering RV function in combination with structure in the clinical interpretation of the athlete's heart.

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Chapter 6

RESEARCH ARTICLE | *Exercise and Cardiac Remodeling in Normal and Athletic States*

Stimulus-specific functional remodeling of the left ventricle in endurance and resistance-trained men

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[1]Cardiff School of Sport and Health Sciences, Cardiff Metropolitan University, Cardiff, United Kingdom; [2]Department of Cardiology, University Hospital of Wales, Cardiff, United Kingdom; and [3]Centre for Heart, Lung, and Vascular Health, School of Health and Exercise Sciences, University of British Columbia Okanagan, Kelowna, Canada

Dawkins TG, Curry BA, Drane AL, Lord RN, Richards C, Brown M, Pugh CJ, Lodge F, Yousef Z, Stembridge M, Shave RE. Stimulus-specific functional remodeling of the left ventricle in endurance and resistance-trained men. *Am J Physiol Heart Circ Physiol* 319: H632–H641, 2020. First published August 9, 2020; doi:10.1152/ajpheart.00233.2020.—Left ventricular (LV) structural remodeling following athletic training has been evidenced through training-specific changes in wall thickness and geometry. Whether the LV response to changes in hemodynamic load also adapts in a training-specific manner is unknown. Using echocardiography, we examined LV responses of endurance-trained ($n = 15$), resistance-trained ($n = 14$), and nonathletic men ($n = 13$) to *1*) 20, 40, and 60% one repetition-maximum (1RM), leg-press exercise and *2*) intravascular Gelofusine infusion (7 mL/kg) with passive leg raise. While resting heart rate was lower in endurance-trained participants versus controls ($P = 0.001$), blood pressure was similar between groups. Endurance-trained individuals had lower wall thickness but greater LV mass relative to body surface area versus controls, with no difference between resistance-trained individuals and controls. Leg press evoked a similar increase in blood pressure; however, resistance-trained participants preserved stroke volume (SV; $-3 \pm 8\%$) versus controls at 60% 1RM ($-15 \pm 7\%$, $P = 0.001$). While the maintenance of SV was related to the change in longitudinal strain across all groups ($R = 0.537$; $P = 0.007$), time-to-peak strain was maintained in resistance-trained but delayed in endurance-trained individuals (1 vs. 12% delay; $P = 0.021$). Volume infusion caused a similar increase in end-diastolic volume (EDV) and SV across groups, but leg raise further increased EDV only in endurance-trained individuals (5 ± 5 to $8 \pm 5\%$; $P = 0.018$). Correlation analysis revealed a relationship between SV and longitudinal strain following infusion and leg raise ($R = 0.334$, $P = 0.054$); however, we observed no between-group differences in longitudinal myocardial mechanics. In conclusion, resistance-trained individuals better maintained SV during pressure loading, whereas endurance-trained individuals demonstrated greater EDV reserve during volume loading. These data provide novel evidence of training-specific LV functional remodeling.

NEW & NOTEWORTHY Training-specific functional remodeling of the LV in response to different loading conditions has been recently suggested, but not experimentally tested in the same group of individuals. Our data provide novel evidence of a dichotomous, training-specific LV adaptive response to hemodynamic pressure or volume loading.

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athlete; echocardiography; heart; left ventricle; remodeling

INTRODUCTION

The theoretical framework for dichotomous structural remodeling of the left ventricle in response to repetitive hemodynamic pressure or volume overload caused by resistance- or endurance-based athletic training was first suggested by Morganroth et al. (36). Despite this hypothesis proposed over 45 years ago, our understanding of the athlete's heart has been largely based upon the resting assessment of left ventricular (LV) structure in highly trained athletes. However, there is growing acceptance that most sport disciplines likely convey a mixed hemodynamic stimulus involving an acute increase in both pressure and volume loading (23, 54). Even so, athletes who demonstrate marked structural adaptations, e.g., increased LV wall thickness, cavity size, and relative wall thickness (41, 42), may also exhibit divergent changes in resting LV function. Several reports indicate that endurance training results in enhanced LV diastolic function (4, 31), possibly due to alterations in blood volume (8), chamber compliance (30), pericardial remodeling (18, 26), and/or underlying cellular adaptation (16, 33). Conversely, strength training has been shown to reduce diastolic function at rest, perhaps due to a reduction in LV compliance resulting from concentric hypertrophy (4, 34). However, greater wall thicknesses in highly trained resistance athletes, and/or those with underlying hypertension, may enhance the heart's ability to maintain stroke volume (SV) when arterial pressure is elevated (46).

Analogous to skeletal muscle (55), even in the absence of structural remodeling, it is possible that chronic exercise training may result in training-specific adaptations in the LV functional response to changes in hemodynamic load. Evaluation of LV longitudinal strain (i.e., myocardial deformation) characteristics alongside conventional volumetric measurements provides the opportunity to simultaneously examine functional LV remodeling and the mechanisms that may explain potential training-specific adaptations. In highly trained, but nonelite, endurance- and resistance-trained men and nonathletic controls, we sought to compare the LV response to *1*) isometric leg-press exercise (i.e., pressure load) and *2*) an intravenous

Gelofusine volume infusion with and without passive leg raise (i.e., progressive volume load). We hypothesized that athletic training would be associated with training-specific adaptation in the LV functional response to a change in load. This would be characterized by a maintenance of stroke volume (SV) in resistance-trained individuals in response to isometric exercise and an augmented SV in endurance-trained individuals when challenged with an increased circulating volume. To investigate the mechanisms responsible for potential training-specific functional remodeling, we conducted a secondary exploratory analysis of changes in LV longitudinal myocardial deformation characteristics in the three groups.

METHODS

Study participants. Nonelite endurance-trained ($n = 15$; runners, cyclists, and triathletes), resistance-trained ($n = 14$; weightlifters and bodybuilders), and nonathletic men ($n = 13$) were recruited to participate in this study. Average weekly training distance was 44 km for runners, 198 km for cyclists, and 158 km for triathletes. All resistance-trained men exclusively performed moderate- to high-intensity full-body resistance training programs and did not engage in any aerobic exercise. Exclusion criteria included the use of cardioactive drugs and prescribed medications; the reported use of performance-enhancing drugs; history of cardiovascular, musculoskeletal, or metabolic disease; or any contra-indications to exercise, asthma, smoking, and competitive performers subject to doping control. All procedures conformed to the ethical guidelines of the 1975 Declaration of Helsinki, with the exception of being registered as a trial. Written, informed consent was obtained from all participants following a detailed explanation of experimental procedures, as approved by the Cardiff School of Sport and Health Sciences Research Ethics Committee.

Study design. Participants were assessed on three separate visits, having refrained from caffeine, alcohol, and vigorous exercise in the preceding 24 h. The first testing session involved the completion of a health and training questionnaire, anthropometric measurements, resting blood pressure measurement, and assessment of a seated leg-press, one-repetition maximum (1RM). After a minimum of 30-min recovery, to assess cardiorespiratory fitness ($\dot{V}O_{2peak}$, peak volume of oxygen consumption), an incremental cycling test was completed. The subsequent experimental visit involved either a pressure load or a volume load, with the final visit involving the second experimental condition. During the pressure-loading visit, transthoracic echocardiographic measurements were obtained at rest and during isometric leg-press exercise at 20, 40, and 60% 1RM, respectively. The volume-loading condition involved a resting echocardiogram before and after an intravenous Gelofusine infusion (7 mL/kg) and again following passive leg elevation to 45° (Fig. 1).

Exercise testing. Resistance exercise was performed on a commercially available leg-press machine (Linear Leg Press, Life Fitness, Ltd., Queen Adelaide, UK). The 1RM protocol for the 45°-inclined double leg press was determined according to the National Strength and Conditioning Association guidelines (3). Participants initially completed a 5 to 10 repetition warm-up against light resistance. After a 2-min rest period, the first attempt was performed using a load that was ~50% of the participants' weight-predicted 1RM. Following a 3–5-min rest, participants repeated the exercise with an increased load. This process was repeated until participants could only perform a single repetition and required between three and five attempts to achieve the correct load. $\dot{V}O_{2peak}$ was determined using an upright incremental test on an electronically braked cycle ergometer (Lode Corival, Groningen). Exercise was started at 50 W for both the resistance-trained individuals and the controls, at 120 W for endurance-trained individuals and was subsequently increased by 20 W every minute until volitional exhaustion. Measurements of ventilatory
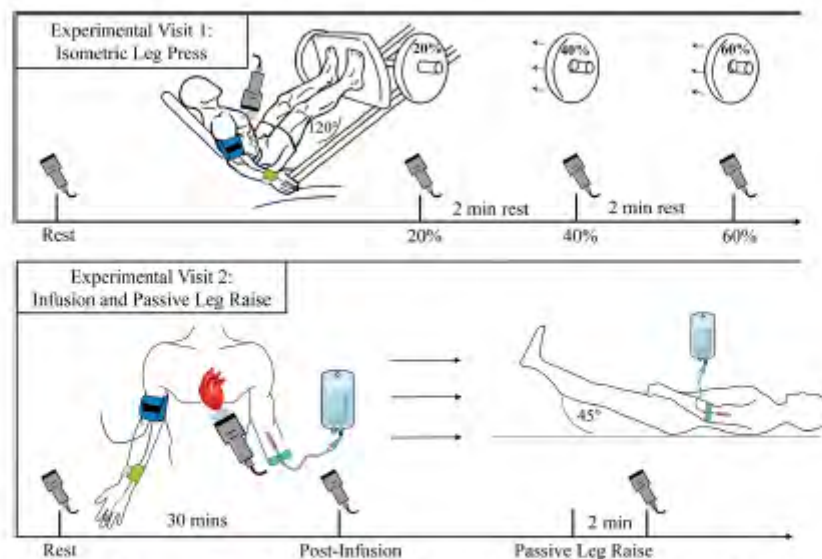

Fig. 1. Schematic of the experimental protocol. *Top*: nonathletic controls and endurance-trained and resistance-trained men performed isometric leg-press exercise at 20, 40 and 60% of 1 repetition maximum. Transthoracic echocardiography (indicated by ultrasound probe) was undergone at rest and during 1 to 2 min of exercise at each load. *Bottom*: on a separate visit, cardiac preload was increased via 7 mL/kg iv Gelofusine infusion and further augmented by a 45° passive leg raise. Echocardiography was performed at rest, postinfusion, and during the passive leg raise. Brachial blood pressure was continuously measured via finger plethysmography, which was calibrated to manual blood pressure obtained at rest. Artwork used with permission.

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gas exchange were obtained using a mask-based, breath-by-breath gas analysis system (Jaeger, Oxycon Pro, Warwickshire, UK). Peak oxygen uptake was defined as the highest $\dot{V}o_2$ over a 30-s consecutive period.

Experimental pressure load. Isometric leg-press exercise was used to elicit progressive increases in systemic blood pressure, as has been previously shown (22, 52). Baseline echocardiographic measurements were obtained with the participant seated on the leg-press machine with legs elevated and feet positioned on the weight-bearing platform. Blood pressure was continuously acquired using finger plethysmography (Finometer PRO; Finapres Medical Systems FMS, Arnhem, The Netherlands) and was calibrated to manual blood pressure obtained at baseline. Individuals were then instructed to push against the weight-bearing platform, maintaining a knee joint angle of 120° for 2 min. Transthoracic echocardiography was performed between the 1st and 2nd min of isometric exercise; individuals were instructed to refrain from performing a Valsalva maneuver throughout each repetition. This protocol was repeated for progressive loads corresponding to 20, 40, and 60% of 1RM, with a 2-min recovery between each effort.

Experimental volume load. Baseline echocardiography was completed with participants in the left lateral decubitus position. Thereafter, an intravenous cannula was inserted and 7 mL/kg Gelofusine (4% succinylated gelatin) was infused over a 30-min period under the supervision of a clinician. Gelofusine was specifically chosen as the infusion substance, instead of saline, as it is maintained in the intravascular space for longer, therefore causing a larger and more consistent volume challenge (32). Heart rate and blood pressure were continuously monitored, and changes in blood volume were calculated according to Dill and Costill (15), using hemoglobin concentration and assuming blood volume preinfusion was 100%. Venous blood was sampled before, midway, and postinfusion and analyzed for sodium (assessment termination criteria, <133 mmol/L), potassium (assessment termination criteria, <3.5 mmol/L), hemoglobin concentration, and hematocrit (assessment termination criteria, <40%) using a handheld point of care device (i-STAT1, i-STAT System, Abbott Point of Care, Princeton, New Jersey). Immediately after the completion of the Gelofusine infusion and subsequent echocardiographic assessment, both legs were passively raised to an angle of 45° for 2 min before further image acquisition to further increase central blood volume.

Transthoracic cardiac ultrasound imaging: resting measures. All transthoracic echocardiography examinations were performed using a commercially available ultrasound machine (Vivid E9, GE Healthcare, Chalfont St. Giles, Bucks, UK) with a 1.5 to 4.6 MHz-phased array transducer (M5S-D, GE Healthcare, Chalfont St. Giles, Bucks, UK). Images were obtained at end expiration following a minimum of 10-min of rest, and the average of three consecutive cardiac cycles were then analyzed off-line using commercially available software (EchoPac version 202, GE, Norway). LV posterior wall thickness (PWT) and internal diameter (LVID$_d$) were measured from the two-dimensional (2-D) parasternal long-axis view at end diastole. Relative wall thickness (RWT) was calculated as $2 \times$ PWT/LVID$_d$. LV mass was calculated according to the cube formula using 2-D imaging (28) and ratiometrically scaled with body surface area (BSA), calculated using the Du Bois and Du Bois (17) formula. LV length at end diastole (LV length$_d$) was determined as the length from the mitral valve annulus to the apical subendocardium from the four-chamber view. LV sphericity index was calculated as LV length$_d$/diameter$_d$ from the apical four-chamber view (14). LV volumes were analyzed using Simpson's biplane approach from the apical four-chamber and two-chamber view by tracing the endocardial border at end diastole and end systole for end-diastolic volume (EDV) and end-systolic volume (ESV), respectively. SV was calculated by subtracting ESV from EDV, and cardiac output was calculated as the product of heart rate and SV. Pulsed-wave Doppler recordings were obtained from an apical four-chamber view to assess transmitral early (E) and late (A)

diastolic filling velocities, with the sample volume placed between the tips of the open valve.

Transthoracic cardiac ultrasound imaging: Experimental measures. LV SV was calculated using Simpson's biplane approach before and after Gelofusine infusion and during the passive leg raise. Due to body position and nature of the strenuous activity during leg-press exercise, we were not able to collect apical two-chamber images in most participants during the experimental pressure loading condition. Therefore, LV volumes were calculated using Simpson's monoplane approach from the apical four-chamber view throughout the leg-press intervention. Transmitral diastolic filling velocities were obtained as described above for each stage of the experimental design.

Global LV longitudinal deformation characteristics, as assessed via strain and strain rate, were acquired from an apical four-chamber view at a frame rate of 60–90 frames/s. All images were analyzed off-line using 2-D speckle-tracking analysis (EchoPac, V202, GE Healthcare). To time align and adjust for inter- and intraindividual variability of heart rate and frame rate, postprocessing was completed as previously described (51). Intraobserver coefficient of variation for myocardial deformation within our group has been previously reported to be between 8 and 11% (49). Frame-by-frame data were exported to bespoke software (2-D Strain Analysis Tool; Stuttgart, Germany), and cubic spline interpolation was applied. The time it took to achieve peak strain and strain rate from the onset of systole was expressed as a percentage of the cardiac cycle, in accordance with previous work (39, 48, 50).

Statistical analysis. All data were first assessed for normality using the Shapiro-Wilk test and visual inspection of Q-Q plots. One-way analysis of variance (ANOVA) was used to compare baseline measures between groups. The changes in hemodynamic and LV deformation measurements that occurred during either the pressure or volume loading conditions were expressed as percent change of the mean values at baseline. Differences in the response between groups were compared using a two-factor, repeated-measures ANOVA (time × training status) with Sidak post hoc analyses. Correlational analyses were used to explore potential relationships between the change in stroke volume and global longitudinal strain characteristics from baseline to the final stage of each condition. All statistical analyses were performed using the Statistical Package for the Social Sciences version 24 (SPSS, Inc.). α was set at $P < 0.05$, and data were expressed as means $\pm$ SD.

RESULTS

Study participants. Baseline characteristics of the study population are shown in Table 1. Lifetime training years and training frequency were not different between the athletic groups. By design, $\dot{V}o_{2peak}$ was higher in those who were endurance trained compared with nonathletic ($P < 0.001$) and resistance-trained men ($P < 0.001$). Additionally, 1RM was significantly greater in the resistance-trained group, compared with both endurance-trained ($P < 0.001$) and nontrained controls ($P < 0.001$). Resting heart rate was significantly lower in endurance-trained men compared with controls ($P = 0.001$); however, no significant differences were observed in resting systolic ($P = 0.791$) or diastolic blood pressures between groups ($P = 0.978$).

Left ventricular structure and function at rest. LV PWT ($P = 0.186$) and sphericity index ($P = 0.514$) were similar between groups. In the endurance-trained group, LV mass/BSA was greater and RWT was significantly lower, compared with controls ($P = 0.017$ and $P = 0.024$, respectively), with no difference observed between resistance-trained men and controls (LVmass/BSA, $P = 0.239$; and RWT, $P = 0.912$, respectively). SV and SV/BSA were significantly greater in endur-

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Table 1. *Baseline participant characteristics*

	Control	Endurance	Resistance	P Values§
n	13	15	14	
Demographics				
Age, yr	23 ± 3	29 ± 5*	24 ± 3†	0.002
Height, cm	180 ± 9	180 ± 6	181 ± 6	0.870
Body mass, kg	75 ± 7	75 ± 6	87 ± 7*,†	<0.001
BMI, m²	23.8 ± 4	23.2 ± 1.7	26.8 ± 1.6*,†	<0.001
BSA, m²	1.94 ± 0.11	1.95 ± 0.11	2.08 ± 0.11*,†	0.004
Body fat, %	15.5 ± 6.3	12.4 ± 4.8	12.5 ± 3.6	0.279
V̇O₂peak, mL·kg⁻¹·min⁻¹	40 ± 5	55 ± 9*	40 ± 4†	<0.001
V̇O₂peak, mL/min	$2,995 \pm 244$	$4,156 \pm 498$*	$3,467 \pm 348$*,†	<0.001
Leg-press 1RM, kg	245 ± 62	275 ± 59	458 ± 38*,†	<0.001
Training history, yr		5 ± 2	6 ± 3	0.543
Training frequency, session/wk	1 ± 1	7 ± 2*	5 ± 1*	<0.001
Hemodynamic				
SBP, mmHg	124 ± 6	122 ± 8	123 ± 8	0.791
DBP, mmHg	76 ± 7	75 ± 7	76 ± 7	0.978
Heart rate, beats/min	58 ± 6	50 ± 6*	56 ± 8	0.017
LV geometry				
LV end-diastolic length, cm	9.2 ± 0.6	9.4 ± 0.6	9.6 ± 0.9	0.476
LV mass, g	136 ± 17	156 ± 16*	158 ± 24*	0.008
LV mass/BSA, g/m²	70 ± 8	80 ± 8*	76 ± 11	0.021
LV PWT, cm	0.81 ± 0.05	0.80 ± 0.05	0.83 ± 0.05	0.186
LV RWT	0.33 ± 0.03	0.30 ± 0.02*	0.32 ± 0.03	0.019
Sphericity index	1.77 ± 0.16	1.79 ± 0.10	1.74 ± 0.16	0.514
LV function				
LV EDV, mL	124 ± 12	155 ± 23*	146 ± 20*	<0.001
LV ESV, mL	48 ± 6	62 ± 11*	58 ± 9*	<0.001
LV SV, mL	76 ± 9	92 ± 15*	88 ± 14	0.007
LV EDV/BSA, mL/m²	64 ± 7	79 ± 11*	71 ± 10	0.001
LV ESV/BSA, mL/m²	25 ± 4	32 ± 5*	28 ± 5	0.001
LV SV/BSA, mL/m²	39 ± 5	47 ± 8*	42 ± 7	0.009
EF, %	61 ± 4	60 ± 4	60 ± 4	0.651
E, cm/s	0.90 ± 0.19	0.90 ± 0.15	0.80 ± 0.15	0.319
A, cm/s	0.41 ± 0.08	0.38 ± 0.06	0.38 ± 0.08	0.803
E/A	2.28 ± 0.47	2.45 ± 0.48	2.12 ± 0.38	0.507
LV longitudinal strain characteristics				
Strain, %	-17.8 ± 2.4	-17.2 ± 1.0	-17.4 ± 2.3	0.716
Strain rate, %/s	-0.95 ± 0.16	-0.84 ± 0.07*	-0.86 ± 0.08	0.048
TTP strain, %	100 ± 5	100 ± 5	98 ± 4	0.582
TTP strain rate, %/s	44 ± 11	47 ± 10	53 ± 10	0.911
Diastolic strain, %	1.61 ± 0.22	1.56 ± 0.21	1.43 ± 0.18	0.802
Diastolic strain rate, %/s	119 ± 3	116 ± 2	119 ± 2	0.197

Values are means ± SD. Hemodynamic and left ventricular (LV) geometry measurements were obtained with the participant rested in the left lateral decubitus position. BMI, body mass index; BSA, body surface area; V̇O₂peak, peak volume of oxygen consumption; 1RM, 1-repetition maximum; SBP, systolic blood pressure; DBP diastolic blood pressure; PWT, posterior wall thickness; RWT, relative wall thickness; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; E, peak early diastolic LV filling velocity; A, peak late-diastolic LV filling velocity; TTP, time-to-peak. §One-way ANOVA. *$P < 0.05$, significant difference vs. control. †$P < 0.05$, significant difference vs. endurance.

ance-trained individuals compared with controls ($P = 0.007$ and $P = 0.009$, respectively). EDV was significantly greater in both endurance ($P < 0.001$)- and resistance ($P = 0.011$)-trained men compared with controls. However, when scaled to BSA, only endurance-trained men had a greater EDV/BSA compared with controls ($P = 0.001$). Similarly, ESV was significantly greater in both endurance ($P < 0.001$)- and resistance ($P = 0.011$)-trained men compared with controls. When scaled to BSA, ESV was only greater in endurance-trained men compared with controls ($P = 0.001$). LV longitudinal strain ($P = 0.716$), time-to-peak strain ($P = 0.582$), and time-to-peak strain rate ($P = 0.911$) were similar between groups at baseline. However, strain rate was significantly greater in controls compared with endurance-trained individuals at rest ($P = 0.048$).

Left ventricular response to incremental pressure load. Heart rate and blood pressure increased to a similar extent during leg-press exercise across all three groups (Table 2). At lower intensities, no differences in SV were observed between groups (20% 1RM; $P = 0.445$; and 40% 1RM; $P = 0.190$). In contrast, the increase in cardiac output at 60% 1RM was significantly greater among resistance-trained individuals compared with controls (92 ± 15 vs. 58 ± 16%, $P < 0.001$). Furthermore, in line with our hypothesis, when challenged with leg-press exercise at 60% 1RM, the resistance-trained group maintained SV closer to baseline values compared with the reduction in SV in controls (Fig. 2A; resistance trained vs. controls, $P = 0.004$). EDV was not different compared with baseline values and remained similar between groups at 20% 1RM; however, at both 40 and 60%, the reduction in EDV was markedly greater in controls compared with both athletic cohorts (Fig. 2B). In contrast, ESV appeared to increase in endurance-trained individuals while remaining relatively constant or minimally decreasing

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Table 2. *Percent change in hemodynamic variables from baseline in response to isometric leg-press exercise*

Variable, %	20% 1RM			40% 1RM			60% 1RM		
	Control	Endurance	Resistance	Control	Endurance	Resistance	Control	Endurance	Resistance
SBP	17 ± 7	18 ± 7	17 ± 7	22 ± 8	24 ± 9	22 ± 7	22 ± 8	24 ± 10	26 ± 7
DBP	16 ± 6	18 ± 9	20 ± 8	23 ± 6	26 ± 10	27 ± 9	25 ± 9	27 ± 12	31 ± 7
Heart rate	52 ± 17	69 ± 35	43 ± 19	77 ± 19	94 ± 39	70 ± 25	86 ± 19	107 ± 52	99 ± 23
Q	47 ± 19	57 ± 31	42 ± 24	67 ± 25	77 ± 42	67 ± 27	58 ± 16	86 ± 51	$92 \pm 15^*$
LV EDV	-2 ± 6	0 ± 8	2 ± 7	-8 ± 9	$-1 \pm 7^*$	$-0 \pm 7^*$	-13 ± 6	$-5 \pm 9^*$	$-3 \pm 7^*$
LV ESV	1 ± 15	11 ± 14	6 ± 14	-9 ± 17	$13 \pm 16^*$	2 ± 16	-8 ± 18	7 ± 16	-3 ± 17
LV SV	-3 ± 9	-7 ± 9	0 ± 9	-6 ± 9	-9 ± 10	-2 ± 9	-15 ± 7	-11 ± 10	$-3 \pm 8^*$
E	15 ± 13	10 ± 16	9 ± 15	30 ± 23	18 ± 16	13 ± 16	39 ± 23	28 ± 22	22 ± 22
A	85 ± 53	97 ± 63	81 ± 35	128 ± 65	140 ± 74	139 ± 83	179 ± 55	167 ± 86	194 ± 92
E/A	-31 ± 17	-40 ± 19	-37 ± 14	-41 ± 21	-49 ± 15	-49 ± 12	-51 ± 7	-47 ± 18	-54 ± 11

Values are means $\pm$ SD. 1RM, 1-repetition maximum; SBP, systolic blood pressure; DBP diastolic blood pressure; Q, cardiac output; LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; E, peak early diastolic LV filling velocity; A, peak late-diastolic LV filling velocity. $^*P < 0.05$, significant difference vs. nonathletic controls at same time point.

in resistance-trained and nontrained individuals (time × training status, $P = 0.086$; supplementary Fig. 1, https://doi.org/10.6084/m9.figshare.12763598). As a result, ESV was different between endurance-trained men and controls at 40% 1RM ($P = 0.038$) and 60% 1RM, though not meeting statistical convention for significance at the higher intensity ($P = 0.088$; Fig. 2C). The pattern of change in transmitral Doppler measures *E*, *A*, and *E/A* across each stage was similar between groups (Table 2).

Secondary correlational analysis of longitudinal deformation characteristics during leg press at 60% 1RM revealed a significant relationship between the change in SV and strain across all individuals ($R = 0.537$, $P = 0.007$; Fig. 3). Subsequent between-group analysis identified a significant delay in the time-to-peak strain in endurance-trained compared with resistance-trained individuals (12 ± 14 vs. $1 \pm 6\%$, respectively; $P = 0.021$). As such, peak longitudinal strain was delayed until after the systolic period in endurance-trained individuals and occurred after 10% of the diastolic period had been completed (i.e., "postsystolic shortening," Fig. 4). However, in nonathletic controls, the $8 \pm 8\%$ increase in time-to-peak strain was not significantly different to either the endurance-trained ($P = 0.522$) or resistance-trained ($P = 0.364$) individuals.

Left ventricular response to volume loading. Gelofusine infusion (7 mL/kg) was successfully completed in 13 endurance-trained (absolute infusion volume; 531 ± 47 mL), 13 resistance-trained (607 ± 51 mL), and 11 control (533 ± 58 mL) participants. Participant noncompliance was due to needle phobia ($n = 1$, resistance trained) and participant attrition ($n = 2$, control; and $n = 2$, endurance trained). Blood volume increased by a similar extent among all groups from pre- to postinfusion (12 ± 3, 12 ± 4, and $13 \pm 4\%$; endurance, resistance, and control, respectively; $P = 0.867$) and blood pressure remained similar between groups throughout the experimental stages (Table 3). Differences in the heart rate response to volume expansion were noted between groups: no change was observed in endurance- and resistance-trained individuals, whereas nonathletic controls experienced an increase of 5 beats/min (Fig. 5), though failing to reach conventional statistical significance ($P = 0.061$).

Contrary to our initial hypothesis, the mean increases in SV following plasma volume expansion were statistically similar between groups and remained comparable following the 45° passive leg raise ($P = 0.350$). However, unlike the

resistance-trained and controls, endurance-trained individuals showed an additional increase in EDV following passive leg elevation after volume expansion (5 ± 5 to $8 \pm 5\%$, $P = 0.018$; Fig. 2B and supplementary Fig. 2, https://doi.org/10.6084/m9.figshare.12763598). ESV remained similar between groups following infusion and passive leg raise ($P = 0.618$). Despite differences in the heart rate response between groups, no significant differences in cardiac output, *E*, *A*, or *E/A* were found between groups (Table 3). Though we found a positive relationship between the change in SV and longitudinal strain across all individuals ($R = 0.334$, $P = 0.054$; Fig. 4), subsequent analysis of longitudinal strain characteristics revealed no between-group differences.

DISCUSSION

The primary findings of this study are that *1*) during high-intensity isometric leg-press exercise, SV is well maintained in resistance-trained men only (Fig. 2A), which may be a consequence of preserved timing of peak LV longitudinal myocardial deformation (Fig. 4); 2) following an acute plasma volume expansion, the increase in EDV and SV are similar between endurance-trained, resistance-trained, and control groups; however, 3) further augmentation of EDV via passive leg raise was only observed in the endurance-trained group (Fig. 2B). To our knowledge, this is the first study to examine the LV functional response to both isometric resistance exercise and increasing circulating blood volume in the same group of individuals. Together, these data support the potential of training-specific functional remodeling of the left ventricle to different stimuli, even in the absence of marked structural adaptations. Furthermore, our data highlight the potential physiological trade-off that may accompany training-specific LV adaptation, whereby the ability to functionally respond to either a volume or pressure load may be at the detriment of managing the alternate stimulus.

Adaptation in the left ventricular functional response to isometric leg-press exercise. In the present study, as has been previously shown (23, 40, 47, 53), well-trained but nonelite resistance-trained individuals did not possess the concentric LV remodeling pattern previously suggested (4, 9, 34, 36, 43). Despite this, the resistance-trained group were better able to maintain SV at near baseline values across each incremental stage of isometric exercise, even with similar increases in
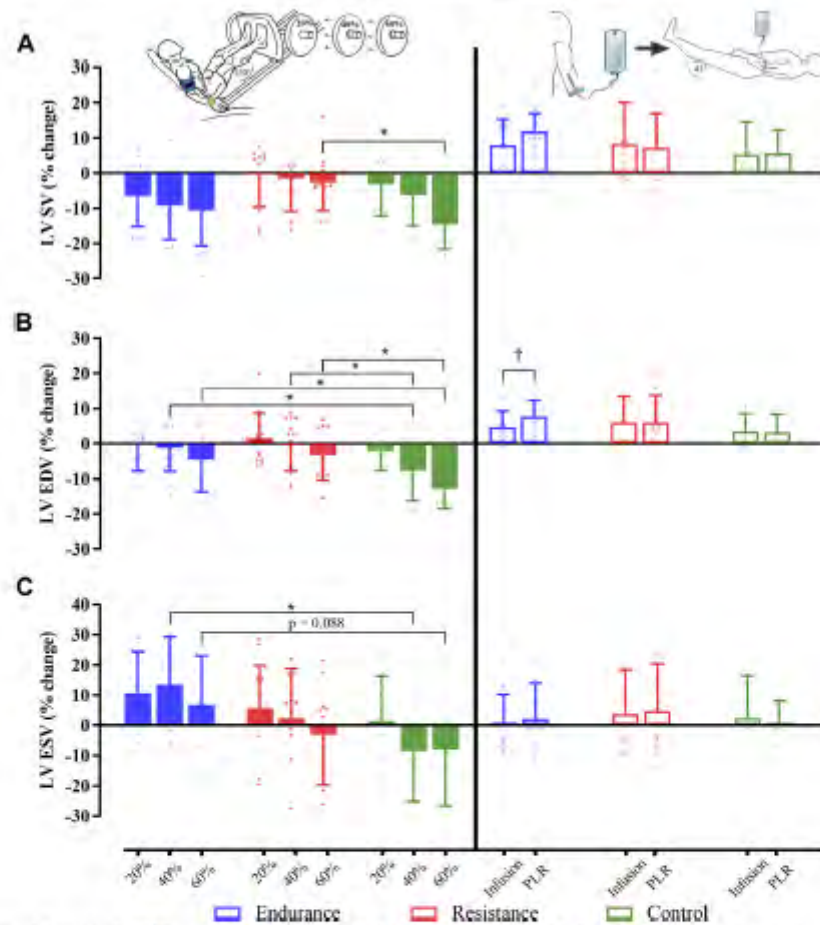
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Fig. 2. Hemodynamic left ventricular (LV) response following static double leg-press exercise at 20, 40 and 60% of 1 repetition maximum (*left*) and following 7 mL/kg iv Gelofusine infusion and combined 45° passive leg raise (PLR; *right*) in endurance athletes (blue; $n = 15$ and $n = 13$ for leg press and infusion condition, respectively), resistance athletes (red; $n = 14$ and $n = 13$, respectively), and nonathletic controls (green; $n = 13$ and $n = 11$, respectively). Data are displayed as percent change from baseline. *A–C*: change in stroke volume (SV; *A*), end-diastolic volume (EDV; *B*), and end-systolic volume (ESV; *C*) following both interventions. *$P < 0.05$, significant difference vs. nonathletic controls at same time point. †$P < 0.05$, significant difference within group between time points ($P < 0.05$). Artwork used with permission.

blood pressure across all groups. In contrast, at 60% 1RM, the endurance-trained group and nonathletic controls experienced a decrement in SV of ~11 and ~15%, respectively.

The mechanisms underlying the divergent LV volumetric response to resistance exercise remain speculative but may involve changes in specific cellular and molecular adaptation of the myocardium and extracellular matrix (16, 33). Cardiomyocyte contractility may increase following resistance training via myosin ATPase activity and enhanced Ca^{2+} influx, as has been shown in rodent studies (12, 19). In turn, these adaptations would increase the force of contraction, thereby improving the myocardial capacity to maintain efficient ejection in the face of an increased afterload. Our secondary analysis of LV longitudinal deformation supports this argument, with our data showing that those with the greatest

increase in myocardial deformation during heavy resistance exercise were better able to maintain stroke volume (Fig. 5A). In contrast, cardiac adaptation with endurance training may have had a detrimental influence on the LV response to isometric exercise. The increase in time-to-peak strain in the endurance cohort is suggestive of a compromised systolic functional response, with a substantial portion of shortening occurring after aortic valve closure, which therefore does not contribute to the ejection of blood and impedes early diastolic relaxation. This pattern of postsystolic shortening of the LV is similar to that previously observed in systemic hypertension (38) and in the right ventricle of healthy populations during an acute increase in pulmonary artery pressure (13, 37, 48). Additionally, while the more compliant chamber of an endurance athlete is beneficial when venous return increases (30),
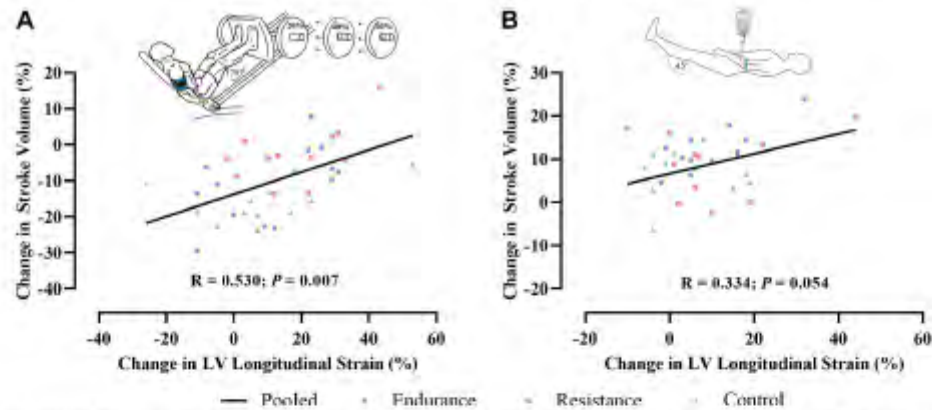
Fig. 3. A: grouped correlation analysis between the change in left ventricular (LV) stroke volume (%) and the change in LV longitudinal strain (%) during 60% 1 repetition maximum leg-press exercise across all individuals (black line). Individual data points represent endurance-trained individuals (blue circles; $n = 15$), resistance-trained individuals (red squares; $n = 14$), and nonathletic controls (green triangles; $n = 13$). B: grouped correlation analysis between the change in LV stroke volume (%) and the change in LV longitudinal strain (%) following combined 7 mL/kg Gelofusine infusion and passive leg raise across all individuals. Individual data represent endurance-trained individuals ($n = 13$), resistance-trained individuals ($n = 13$) and nonathletic controls ($n = 11$). Artwork used with permission.

greater chamber compliance may cause a disproportionately larger decrease in SV when venous return is reduced, for example, during some forms of isometric exercise (1). The heterogeneous EDV response and relative maintenance of SV in resistance-trained individuals may also be related to differential cardiopulmonary interactions between the groups. Abdominal pressure, intrathoracic pressure, right atrial pressure, and lung volumes are likely to have increased during leg-press exercise, thereby reducing venous return (1, 7). Indeed, the decrease in SV in controls was accompanied by a reduction in EDV, suggestive of an underfilling of the LV, which differs mechanistically to endurance athletes, in whom a decrease in SV appears to be driven by an increase in ESV. This elevation in ESV may reflect a compromised ability to maintain systolic performance during an acute afterload challenge, reflected by a significant increase in postsystolic shortening. The additional residual volume in the ventricle after ejection, combined with

venous return, likely moderates the reduction in EDV in the endurance-trained group, compared with controls. As recently proposed by Shave et al. (46), it is possible that the divergent hemodynamic stimuli brought about by chronic endurance and resistance training leads to differential cardiac adaptations, which compromise the heart's ability to accommodate the alternate volume or pressure challenge. Our data further support this contention, highlighting a potential physiological trade-off in the endurance athlete's capacity to cope with increasing systolic pressure. Other multimodality, mechanistic investigations in rat hearts have shown that while resting LV functional measures are relatively unchanged by intense lifetime exercise, because of the disproportionate increase in right ventricular (RV) wall stress during intense exercise (27), the RV may be more susceptible to detrimental remodeling at the extremes of exercise load (45). Further research is warranted to examine both the mechanisms responsible for our divergent
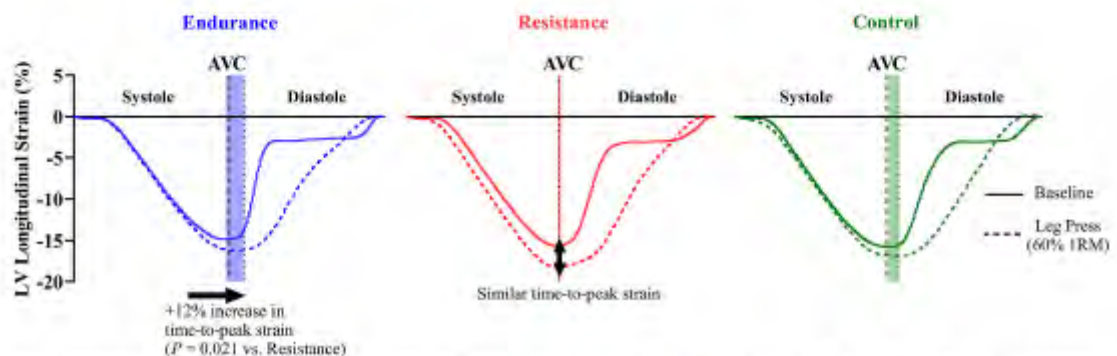

Fig. 4. Temporal representation of left ventricular (LV) strain between groups at baseline (solid line) and during 60% 1 repetition maximum (1RM) leg-press exercise (corresponding dashed line) in endurance-trained individuals (blue, $n = 15$; left), resistance-trained individuals (red, $n = 14$; middle), and nonathletic controls (green, $n = 13$; right) and pooled data (black). Shaded area after aortic valve closure (AVC) represents postsystolic shortening following leg-press exercise as a percentage of the cardiac cycle.

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Table 3. *Percent change in primary variables from baseline in response to 7 mL/kg iv Gelofusine infusion and subsequent passive leg raise*

Variable, %	Infusion			Passive Leg Raise		
	Control	Endurance	Resistance	Control	Endurance	Resistance
SBP	0 ± 6	−1 ± 4	−2 ± 5	−4 ± 12	3 ± 10	0 ± 7
DBP	−3 ± 10	3 ± 8	−1 ± 9	1 ± 9	3 ± 5	2 ± 10
Heart rate	6 ± 9	−2 ± 9	0 ± 8	9 ± 10	0 ± 11	0 ± 11
Q	12 ± 15	7 ± 13	8 ± 14	15 ± 12	12 ± 14	8 ± 16
LV EDV	4 ± 5	5 ± 5	6 ± 7	3 ± 5	8 ± 5‡	6 ± 8
LV ESV	2 ± 14	0 ± 10	4 ± 14	0 ± 8	2 ± 12	5 ± 16
LV SV	5 ± 9	8 ± 7	8 ± 12	5 ± 7	12 ± 5	7 ± 10
E	12 ± 12	10 ± 26	15 ± 16	11 ± 11	18 ± 22	18 ± 23
A	12 ± 12	7 ± 23	18 ± 24	15 ± 24	11 ± 21	18 ± 33
E/A	4 ± 19	10 ± 32	1 ± 15	−2 ± 15	11 ± 21	−1 ± 20

Values are means ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; Q, cardiac output; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; E, peak early diastolic LV filling velocity; A, peak late diastolic LV filling velocity. ‡$P < 0.05$, significant difference within group between time points.

results and also functional RV remodeling in response to hemodynamic perturbation.

Adaptation in the left ventricular functional response to an increased circulating blood volume. Previous studies using lower-body negative pressure and saline infusion to manipulate cardiac preload have shown that for any given LV filling pressure, endurance athletes have a greater EDV (30). The findings from this seminal study indicate that endurance athletes have greater LV chamber compliance compared with that in sedentary controls. Consistent with these findings, we also found that endurance-trained individuals, unlike resistance-trained individuals and healthy controls, were capable of further EDV augmentation (through passive leg elevation) even when already volume expanded. Within the methodological confines of the present study, it is difficult to ascertain the acute limitation to ventricular filling between groups, though it likely reflects a dependency on both the compliance characteristics of the myocardium and pericardial constraint (26). It is possible that the "tightness" of the pericardium ultimately limits ventricular filling and that pericardial remodeling (18), subsequent to the repetitive increases in circulating blood volume associated with prolonged training, may explain the ability for endurance-trained individuals to "accept" a greater EDV.

Interestingly, while cardiac output increased across all groups following volume loading, this was achieved via increased SV in athletic populations compared with an augmentation of heart rate with preserved SV in controls (Fig. 5). Following 30 mL/kg saline infusion, Levine et al. (30) also observed a significant elevation in heart rate in nonathletes, by 12 beats/min ($P < 0.01$), but not in endurance athletes (7 beats/min; $P > 0.05$). This chronotropic sensitivity in untrained individuals may be due to mechanical factors, such as reduced cardiac chamber compliance (6, 30) and peripheral vascular distensibility (2, 44), or perhaps due to intrinsic pressure receptor reflexes (5, 35). It is unlikely, however, that this is a response of a single autonomic reflex, but rather a reflection of the complex relationship between baseline autonomic tone (11), sinoatrial remodeling (10), pressure receptor reflexes (21), and/or altered stretch receptor sensitivity (20).

Study limitations. There are several limitations that must be acknowledged. First, we recognize that the small sample size is a significant limitation; however, this is the first study to compare the LV response to incremental pressure and volume perturbations in the same group of differentially trained individuals. Further investigation of sport-specific functional LV remodeling is warranted in a larger cohort and should also
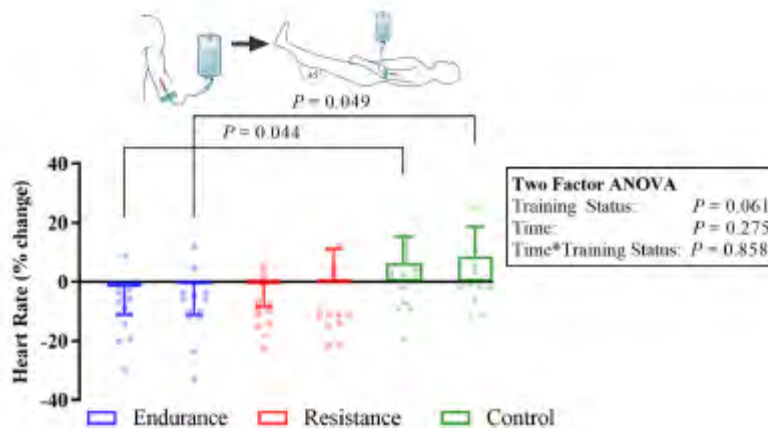

Fig. 5. Heart rate response (%change) following 7 mL/kg Gelofusine infusion and subsequent passive leg raise in endurance-trained individuals (blue circles; $n = 13$), resistance-trained individuals (red squares; $n = 13$), and healthy controls (green triangles; $n = 11$). Data are displayed as percent change from baseline. Artwork used with permission.

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consider responses in individuals with substantial cardiac remodeling. We did not capture a detailed history of training intensity and therefore cannot discern the influence of overall training load. Additionally, we acknowledge that the endurance-trained cohort was older than those resistance trained; however, controlling for age as a covariate did not alter the findings of this study. We used isometric exercise performed without a Valsalva maneuver to facilitate data collection; however, this exercise is unlikely to perfectly reflect the typical training conditions of resistance athletes. Furthermore, from our data and others (1, 22, 29), it is evident that certain forms of resistance exercise, including heavy leg press, can cause LV underfilling. As such, different forms of resistance exercise may influence preload as well as afterload, which may be relevant for physiologic adaptation. In the present study, it is difficult to ascertain the mechanisms that underpin the preserved LV filling in resistance-trained individuals and whether this is due to a difference in cardiopulmonary interaction and subsequent modulation of LV filling, or enhanced LV deformation. Additionally, data reported are only relevant for young healthy men. Specific studies to examine the female athlete's heart, which are adequately powered to explore sex differences, are needed and have been undertaken by our group (56) and others (24, 25).

Conclusion. This study provides novel data that support the potential of stimulus-specific functional remodeling of the LV, even in the absence of marked structural adaptations. In response to a marked hemodynamic pressure load, resistance-trained individuals better maintained SV, which was coupled with preserved longitudinal deformation characteristics. Conversely, in a volume-loaded state, only endurance athletes were capable of further increasing EDV. Further research is warranted to examine the mechanisms that underpin these training-specific differential responses.

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