Bionic women and men

Heart failure and an artificial heart pump

Left ventricular assist devices (LVADs) have been developed for heart failure patients when medicine does not work and a transplant is unavailable. These devices provide a continuous flow of blood around the body, creating 'humans without a pulse', and thus presenting a unique opportunity to examine blood flow and heart function in relation to overall health. Dr Eric J. Stöhr, of Cardiff Metropolitan University, UK, and Columbia University, USA, is a key member of the HIT-LVAD trial team (led by Dr McDonnell in Cardiff and Prof Colombo in NYC), a research project aiming to understand the biology of LVAD patients and using the insights to benefit the patients' health and the general public.

The heart is fundamental to our circulatory system. When it is healthy, it is roughly the size of a fist and sits in the middle of the chest, slightly to the left. Comprised of two interacting sides, separated by the septum, each are similar in having two compartments, the atria and ventricles. Blood enters the atria when they relax while the ventricles simultaneously contract and pump blood out into the aorta on the left side, or pulmonary artery on the right. When the ventricles relax, they fill while the atria assist this filling by contracting and moving blood into the ventricles. Valves between the atria and ventricles stop blood from flowing back in the wrong direction.

Although the two sides of the heart are generally similar in form, they differ in size and anatomy because of their function. The right-hand side is smaller than the left, it pumps blood through the pulmonary circuit, returning low-oxygen blood to the lungs to replenish the blood with oxygen. The left-hand side is larger, as it has the harder job of pumping oxygen-rich blood through the high-pressure circuit around the body to cells, tissues and organs.

The left ventricle is comprised of a muscle fibre arrangement that represents a wound, double helix.

An examination of the anatomy of each of the four chambers reveals interesting differences, with the left ventricle – the largest chamber – the most complex of all. In a healthy person, it is comprised of a muscle fibre arrangement that represents a wound, double helix. A helix can be best imagined as a mechanical spring, with the interesting property of being either right- or left-twisting, no matter which way you turn it; a right-handed helix cannot be superimposed over a left-handed one. The left ventricle has two opposite helices arranged over three layers. The inner layer, the subendocardium, is arranged as a right-handed helix, which transitions to the middle circumferential layer. In turn, this transitions to the subepicardium, the surface layer, which is arranged as a left-handed helix. This anatomy gives the left ventricle the property of twisting when it contracts, a motion that is comparable to the wringing of a towel.

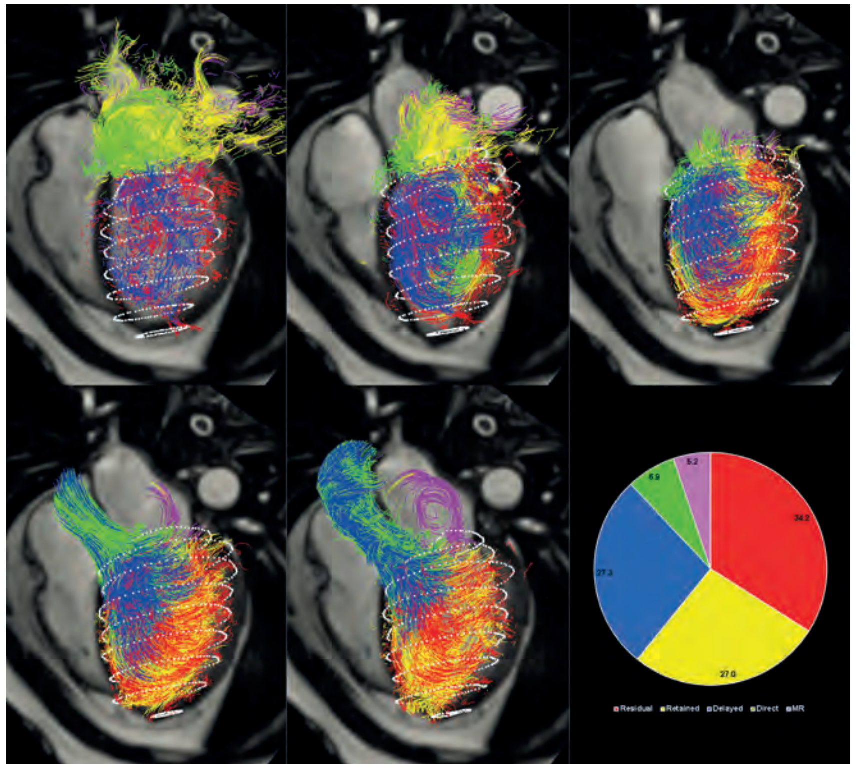
THE EFFICIENCY OF THE HELIX TWIST

The helical arrangement of muscle fibres in the left ventricle is reminiscent of spiral and vortex patterns in nature, which can range from the small to the astronomical, for example, the structure of our DNA, whirlpools, hurricanes, and the rotational patterns of our solar system and other galaxies. It is an anatomical feature that is found across the evolution of various animal species and has fascinated anatomists over the centuries.

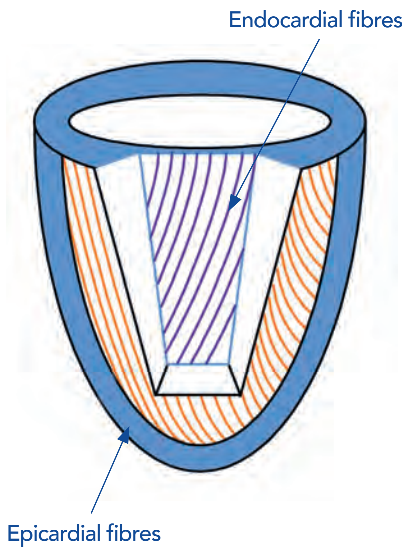
Vortex patterns link two fundamental forms of motion that work in close balance with each other; an inner, rapidly descending swirl and an outer, less rapid, ascending rotation. Such motions produce energy-efficient suction and expulsion forces that have been exploited by humans in the design of propellers and turbines. In the heart, this helical shape helps the ejection of blood as the muscle twist (or "wrings") during contraction. Experimental and mathematical modelling of the clockwise and anticlockwise spiral loops of muscle fibres in the left ventricle has shown that it is also an efficient way of distributing stresses and strains across the chamber. When the heart muscle relaxes, a rapid 'untwisting' occurs, which is thought to help with the refilling of the chamber.

EVALUATING A 'NORMAL' TWIST

The relationship between systolic twist (contraction) and diastolic untwisting (relaxing) of the heart, and how they relate to cardiovascular health and disease is not clearly understood. What we do know is that people with chronic heart disease can have significantly altered left ventricle twist mechanics, with several factors contributing to this. High blood pressure, congenital heart conditions or diseases affecting the valves in the heart can all increase blood pressure and volume, causing injury to the heart. In turn, this can change its shape, size and structure, leading to a progressive decline in left ventricular performance. Reduced blood flow to the heart from blocked arteries can also distort the efficiency of the filling and emptying dynamics, as can an alteration to the electric pulse controlling the contraction of the heart's muscle fibres.



Result of flow component analysis using particle tracing of a patient with mitral valve regurgitation. Displayed path lines are colour coded according to flow component classification. Top row from left to right start of early filling, peak early filling, end diastole; Bottom row early systole, late systole, pie depicting the percentage of LV for each of the five defined flow components. Regurgitant jet results in recirculating flow pattern in the left atrium. This figure was previously published in 'Advanced Analysis Techniques for Intra-cardiac Flow Evaluation from 4D Flow MRI', Rob J. van der Geest and Pankaj Garg2, *Curr Radiol Rep* (2016) 4: 38. https://doi.org/10.1007/s40134-016-0167-7 and is under the Creative Commons Attribution 4.0 International Licence (http://creativecommons.org/licenses/by/4.0/).



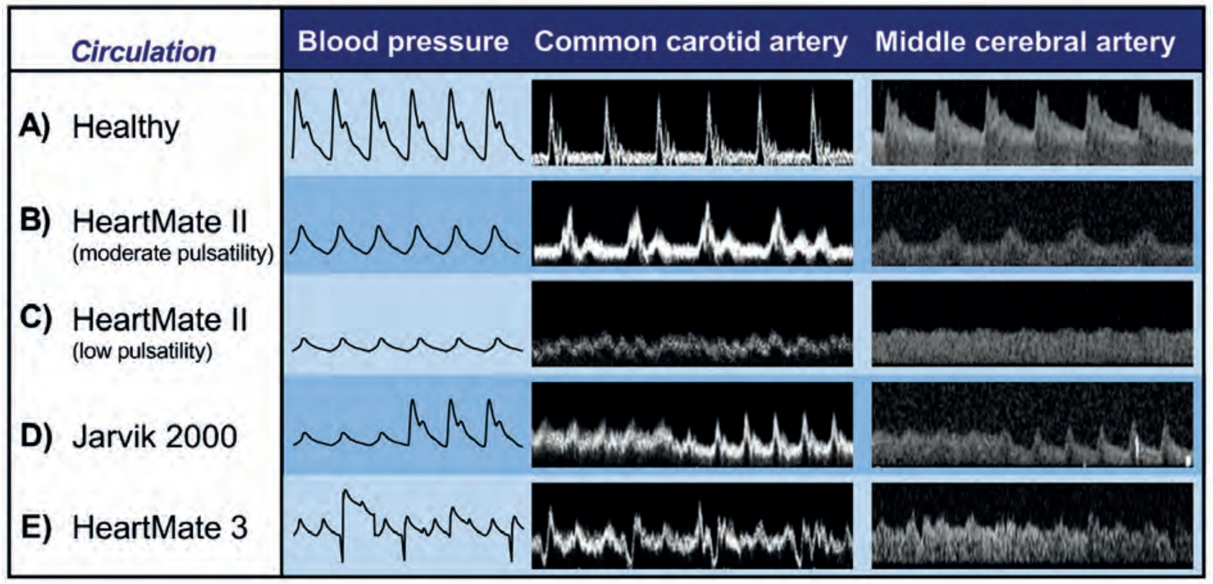
Helixes and twist in the left ventricle (LV). LV endocardial and epicardial helix configuration in end diastole. This figure was previously published in the paper 'Left ventricular twist mechanics in the context of normal physiology and cardiovascular disease: a review of studies using speckle tracking echocardiography'. (2016). Eric J. Stöhr, Rob E. Shave, Aaron L. Baggish, and Rory B. Weiner. *Am J Physiol Heart Circ Physiol* 311: H633–H644. doi:10.1152/ajpheart.00104.2016.

In a recent review of research assessing left ventricle dynamics in both healthy people and those with cardiac issues, Dr Eric J. Stöhr, a Marie-Skłodowska-Curie Fellow of the European Union and lecturer in Cardiac Physiology and Health at Cardiff Metropolitan University, UK, highlights evidence to show that left ventricle twist dynamics can also alter with ageing, as well as through exercise. However, these effects have received much less attention than those from cardiovascular disease. He argues that understanding the left ventricle twist response to normal physiological challenges is essential for interpreting the effects of heart conditions. Essentially, we need to fully understand normal cardiac function to appreciate the influence of cardiovascular diseases. Research is ongoing to understand why and how left ventricle twist is altered in various cardiac conditions and across the age and health range of the general population.

LEFT VENTRICULAR ASSIST DEVICE

Unfortunately, an increasing number of individuals do not have normal heart function, including twist. This globally growing prevalence of heart failure can be attributed to the combination of an ageing population and substantial improvements to medicines prolonging the life of people with heart disease. In America alone, over 5 million people suffer from heart failure and there is a significant proportion- 150,000 to 250,000 – whose condition will worsen despite medicinal advancements. Currently, the optimal treatment for these patients is a heart transplant, but with a shortage of donors, this is not always possible. In 2016, only 2800 patients underwent a heart transplant operation in the USA. To fill this gap, a mechanical pump, the left ventricular assist device (LVAD), has been developed to support the failing muscle tissue of the heart.

The LVAD works by sucking blood out of the sick heart and moving it back to the normal circulation, generating enough cardiac output to service the cells, tissues



Arterial blood pressure waveforms and blood flow in the common carotid artery (CCA) and middle cerebral artery (MCA) of representative healthy and left ventricular assist device (LVAD) patients. In the healthy circulation, blood pressure and CCA blood flow are pulsatile, which is somewhat reduced but still clearly present in the MCA. b HeartMate II with low pump speed has a moderately reduced pulse pressure and pulsatility. c HeartMate II with high pump speed has significantly reduced pulse pressure and pulsatility. d Jarvik 2000 with the transition from high to low pump speed occurring every minute for a few seconds. e HeartMate 3 with sequential changes in pump speed occurring every 2 s (0.15 s of reduced speed by 2000 rpm below baseline and 0.20s of increased speed by 2000 rpm above baseline), also termed "artificial pulse". This figure was previously published in 'The Unique Blood Pressures and Pulsatility of LVAD Patients: Current Challenges and Future Opportunities' from Castagna, F., Stöhr, E.J., Pinsino, A. et al. Curr Hypertens Rep (2017) 19: 85. https://doi.org/10.1007/s11906-017-0782-6 and is under the Creative Commons Attribution 4.0 International Licence.

and organs of the body. Its installation requires open-heart surgery, where one end of the device is attached to the left ventricle and the other end to the aorta. Blood flows from the ventricle into the LVAD, which then pumps the blood out into the aorta to flow around the rest of the body. A cable called a driveline extends from the pump, out through the skin, connecting the pump to a controller and power sources worn outside the body. A significant number of patients that are either ineligible for a donor's heart or are awaiting the availability of a suitable heart are implanted with an LVAD. Over the past decade, close to 20,000 patients have been supported by this device as either a temporary substitute or long-term alternative to heart transplant.

The first generation of LVADs were pulsatile devices, designed to mimic the pumping action of the heart, but they were large and had limited durability. The second generation LVADs provide a continuous flow of blood around the body. They consist of an inflow cannula that sits in the left ventricular cavity, a pump impeller that rotates at a constant pre-set speed and an outflow graft that continuously delivers blood into the aorta, to support the whole cardiac cycle.

LVAD CHALLENGES

Evidence shows that very sick heart failure patients fitted with continuous-flow LVADs have a much-improved survival, but some also experience complications, such as gastrointestinal bleeding, thrombosis and stroke. Although strong evidence is currently missing, these issues have been linked to the lack of pulse provided by these devices. One of the very latest third generation LVAD devices, the Heartmate 3, provides an artificial pulse through intermittent swings in flow. However, despite producing better health outcomes than its predecessors, patients fitted with this new device still suffer from stroke and gastrointestinal problems commonly seen in other LVAD patients. It is possible that the correct measurement of blood pressure in patients using Heartmate 3 could be key to reducing a significant number of these adverse effects.

Other challenges surrounding LVADs include the monitoring of blood pressure, understanding the effects on our physiology, including the brain, eye and kidneys and further health improvements of these patients. The medical technology industry is tackling the more technical challenges of LVADs; creating a device so small that it can be fully implanted in the chest (like a pacemaker) without needing a driveline connecting to batteries outside the body.

HIT-LVAD TRIAL

With the number of continuous-flow LVAD patients expected to markedly increase over the next number of decades, it is important for research to provide an in-depth understanding of the optimal LVAD settings. Understanding how continuous-flow LVADs affect the circulatory system and organs may provide important information on how the pulse and flow can be modified to each patient, thereby further increasing patients' health when living with these machines.

The HIT-LVAD trial is an exciting new collaboration between researchers at Cardiff Metropolitan University, UK and Columbia University Irving Medical Center, NYC, USA. Designated a Marie Skłodowska-Curie Global Research Fellow, Dr Stöhr has been seconded to Columbia University from Cardiff to work with a team of world-leading heart failure specialists, academics, patients and industrial partners.

Researchers have the opportunity to study blood flow in a way that has not been possible to date.

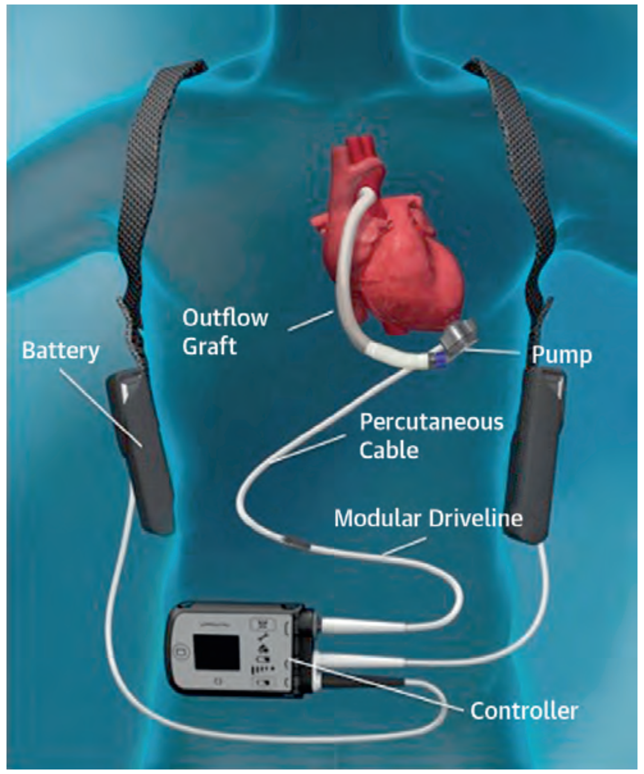
The aim is to better understand the risks and causes of adverse effects associated with patients fitted with continuous-flow LVADs. It will be the first time in human history that researchers have the opportunity to study blood flow in a way that has not been possible to date.

A UNIQUE OPPORTUNITY

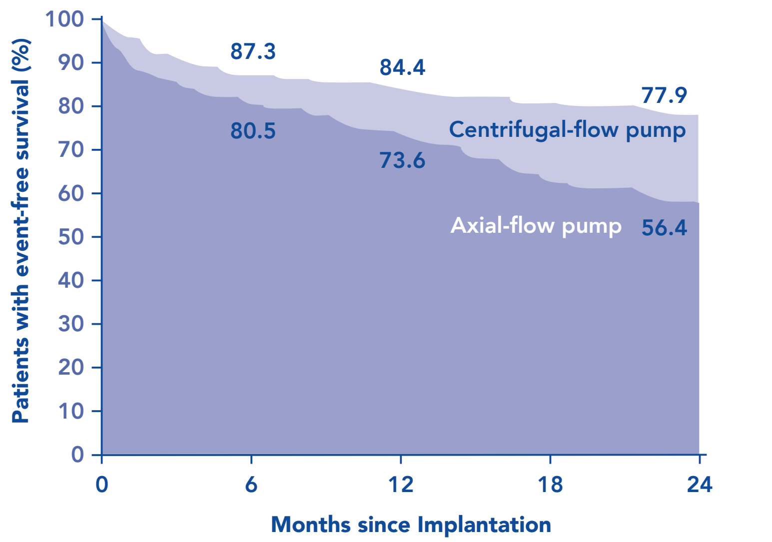
The second and third generation LVADs have improved the longevity of heart failure patients, but people who live with the aid of some of these machines have the peculiar characteristic of being left without a pulse. This has raised several intriguing questions about our physiology. Do we really need a pulse? If so, what are the effects of short- or long-term loss or reduction in arterial pulse pressure? The HIT-LVAD trial hopes to apply insight from research on this area, using the LVAD patient population, to increase our understanding of more general cardiovascular disease such as high blood pressure.

A stepping-stone towards this goal is the development of a reliable method of monitoring blood pressure. Elevated blood pressure has been associated with continuous-flow LVAD-related complications. Since LVAD patients do not have a strong pulse or none at all, normal blood pressure measurements are very difficult to assess, being limited to hospitalised patients whose readings are taken via an invasive arterial catheter. The Heartmate 3 system offers an additional challenge since it incorporates artificial pulse technology and therefore interrupts the regular flow in an unpredictable manner. Together with collaborators from industry and academia, Dr Stöhr has confronted this challenge by testing and validating a new machine, the Mobil-O-Graph system. The Mobil-O-Graph monitor offers a good non-invasive method of measuring blood pressure in HeartMate II patients, and current efforts continue to increase its accuracy compared with blood pressure readings from invasive arterial catheters.

Further HIT-LVAD research will measure the blood flow and pulse in different LVAD patients in the aorta, the neck (carotid arteries), the eye (retinal arteries) and brain (middle cerebral arteries), with the aim of increasing our understanding of which machine and machine settings are best for the health of the LVAD patient. This cutting-edge research will be used to improve the lives of heart failure patients undergoing LVAD implantation all over the world, and ultimately, increase our knowledge of optimal blood flow and heart function in relation to overall health for the whole population.



The Fully Magnetically Levitated LVAS. The blood pump is positioned within the pericardial space, with its integral inflow conduit in the left ventricle and outflow graft attached to the ascending aorta. The percutaneous power cable is tunnelled through the abdominal wall and is attached to the system controller that receives power from 2 lithium-ion batteries. LVAS ¼ left ventricular assist system. This figure was previously published in 'Fully Magnetically Levitated Left Ventricular Assist System for Treating Advanced HF', Ivan Netuka et al, *Journal of the American College of Cardiology, Elsevier*, Volume 66, Issue 23, 15 December 2015, Pages 2579-2589, https://doi.org/10.1016/j.jacc.2015.09.083 and is under the Creative Commons License CC BY-NC-ND 4.0.



The graph shows that the newer heart pump, the centrifugal-flow pump, appears to have improved the survival of heart failure patients (top numbers). Current research such as the HIT-LVAD trial is determining why this may be the case, as it has previously been suggested that an added 'pulse' may have beneficial effects. This figure was recreated from the paper 'A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure', (2016), *The New England journal of medicine*, 376;5. pp 440-450.

Behind the Research

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Research Objectives

Dr Stöhr's research focuses on understanding the interaction between heart muscle dynamics and arterial function in health and disease.

Detail

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Bio
Eric Stöhr trained in exercise science and obtained his PhD in human cardiovascular physiology.

Funding
Barry J McDonnell and Eric J Stöhr have received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 705219 ["HIT-LVAD trial"].

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- **Prof Paolo Colombo.** Director, Center for Advanced Cardiac Care, Columbia University Irving Medical Center, New York City, New York, USA.
- **Dr William Cornwell.** Assistant Professor of Medicine-Cardiology, University of Colorado.
- **Dr Keiichi Itatani.** Cardiovascular Surgeon, Endowed chair, Department of Cardiovascular Surgery, Cardiovascular Imaging Research Center, Kyoto Prefectural University of Medicine.
- **Dr Barry McDonnell.** Reader, Cardiff Metropolitan University, Cardiff, UK; PI of the HIT-LVAD trial.
- **Prof Yoshifumi Naka.** Cardiovascular Surgeon, Professor, Department of Cardiothoracic Surgery, Division of Surgery, Columbia University Medical Center.
- **Dr Hiroo Takayama.** Cardiovascular Surgeon, Associate Professor, Department of Cardiothoracic Surgery, Division of Surgery, Columbia University Medical Center.
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- **Uwe Korth (CEO IEM).** CEO of IEM (www.iem.de/en/).
- **Achim Schwarz.** (www.alf-distribution.com/en/)

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Personal Response

Prof Colombo, you have facilitated Dr Stöhr's & Dr McDonnell's work in New York – The HIT-LVAD trial is an exciting collaboration between leading researchers. What excites you most about this project?

" First, because transatlantic collaborations like the HIT-LVAD trial are rare. Second, because LVAD is an exciting technology that is revolutionising the way cardiologists treat patients with advanced heart failure. LVADs have undergone tremendous improvements over the past decades, from bulky, noisy pumps with a limited durability of 1 or 2 years, to smaller, silent and more durable pumps with a durability of several years, even more than 10 years. Separate clinical studies in Europe and the US indicate that the recently developed HeartMate3 appears to overcome life-threatening complications because it does not clot. The collaboration between European and US researchers is therefore essential for further developments. "

Cardiff Metropolitan University | Prifysgol Metropolitan Caerdydd

Columbia University in the City of New York