British Heart Foundation

Pumping progress

Impact of British Heart Foundation (BHF) support for heart failure research

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Impact thematic review

Contents

Impact of BHF support for heart failure research

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1) Introduction

Heart failure is the inability of the heart to maintain adequate circulation of blood in the body. It is often the culmination of many acute and chronic cardiovascular diseases. Heart failure has been described as a pandemic, affecting at least 64 million people worldwide, with numbers increasing [1]. This can be attributed to an ageing population, advancements in cardiovascular treatments that enhance survival rates, and the availability of therapies that extend the lives of heart failure patients. It's estimated that over one million people in the UK have heart failure[1].

The most common causes of heart failure include heart attack, high blood pressure, heart valve disease, and cardiomyopathy. Heart failure can also be caused by diabetes, viral infections affecting the heart muscle, congenital heart problems, abnormal heart rhythm (arrhythmia), some cancer treatments, amongst other things. In some cases, the cause of heart failure is unknown.

Heart failure has been historically classified in many ways, according to severity, symptoms, ejection fraction (% of blood that is pumped out with each heartbeat), and others. It can be described as acute, when symptoms appear suddenly; or chronic, when heart failure is a long-term condition. Chronic heart failure (CHF) is characterised by the risk of acute deterioration, often requiring hospital admission.

Heart failure may be classed as:

- Heart failure with preserved ejection fraction (HFpEF) (>50%), where a patient has signs and symptoms of heart failure despite their heart maintaining a normal or near normal pumping function (affecting around 16% of heart failure patients)[2]

[1] https://www.bhf.org.uk/-/media/files/for-professionals/research/heart-statistics/bhf-cvd-statistics-uk-factsheet.pdf

- Heart failure with mildly reduced ejection fraction (HFmrEF) (>40% - 49%), seen as an intermediate type of HF where a patient's heart pumping function is slightly reduced (affecting around 24% of patients)[2]
- Heart failure with reduced ejection fraction (HFrEF) (<40%), where a patient's heart pumping function is reduced meaning the amount of blood being pumped out is less than the body needs (affecting around 60% of patients)[2]

Coronary heart disease is the primary cause of HFmrEF and HFrEF, whereas the underlying diseases of patients with HFpEF often consist of hypertensive heart disease and heart valve disease.

Heart failure is rampant in the elderly and affects quality of life. Symptoms include shortness of breath, fatigue, and swelling of the feet and ankles which can spread to the lower body. Around half of those diagnosed with heart failure in the UK die within five years of their diagnosis[3].

No cure exists for heart failure, apart from a heart transplant in a small number of cases. Treatments aim to control the symptoms and slow down progression of the condition. In addition to healthy lifestyle changes, the main treatments for heart failure include medication, a pacemaker or ICD, and heart surgery.

British Heart Foundation (BHF) has funded heart failure research since the 1970s, with more than £140 million worth of grants. This has led to advances in the diagnosis, treatment and management of heart failure.

2) Generating new knowledge

a) Mechanisms of heart contraction

As heart failure is a disease where the heart stops pumping blood efficiently throughout the body, it was essential to better understand how the heart contracts in the first place. This knowledge is necessary to find out what goes wrong in heart failure and to help identify treatments.

The heart contracts through a coordinated electrical signal that triggers heart muscle fibres to contract in a synchronized way. The coordinated contraction and relaxation of the heart chambers create the rhythmic beating that keeps blood flowing throughout the body.

I. Electrics of heart contraction

The role of calcium

Calcium plays a crucial role in the process of heart contraction. At the end of the 1970s, it was discovered that the electric signal that triggers a heart contraction causes 'voltage-gated calcium channels' to open in heart muscles cells, triggering an influx of calcium inside the cells. The calcium in the cells then binds

to proteins on heart muscle filaments to initiate muscle contraction. This process, known as calcium-induced calcium release, was identified as the predominant mechanism for cardiac excitation-contraction coupling. The research community then started to investigate the importance of this mechanism in heart disease, and in heart failure in particular[4], to provide a functional explanation for the disease and identify potential target(s) for treatment.

The establishment of robust protocols for the isolation of cardiomyocytes (heart muscle cells) from human biopsies and animal models, and the application of fluorescence and microelectrode techniques have favored a significant amount of research in the UK. BHF has funded a substantial portion of research aimed at understanding the cellular and molecular mechanisms of calcium homeostasis in the context of heart failure.

The role of the sarcoplasmic reticulum (a major source of intracellular calcium) and the mechanism of heart muscle relaxation in heart failure were an integral part of the work of many BHF-funded researchers at Imperial College London and the Universities of Glasgow, Leeds, Manchester and Oxford. The specific areas of investigation have been the expression and regulation of key proteins involved in calcium regulation. These proteins include SERCA[5, 6] NCX[7] and RYR[8] with specific discoveries on mechanisms of phosphorylation, spontaneous calcium release (calcium sparks) and microdomain regulation of calcium (transverse tubule) in heart failure.

While drugs targeting the calcium pathway can be used in the treatment of heart failure, they are usually not the first line of treatment and are used in specific conditions (e.g. heart failure caused by hypertrophic cardiomyopathy). Researchers around the world continue to study the role of calcium in heart failure, in the hope of developing more targeted therapies. In 2021, BHF funded Professor Andrew Trafford and Dr Mohammed Obeidat at the University of Manchester to understand the role of calcium buffers (molecules that help regulate the concentration of calcium ions within cells) in heart failure. They want to find out whether targeting them could improve heart contraction.

Other ions:

Other ions, particularly sodium and potassium, also play significant roles in the electrical and mechanical activities of the heart.

BHF funded Professor Michael Shattock and his team at King's College London to study the relevance of the Na/K ATPase (sodium-potassium pump) and its regulation in heart failure. The protein acts as a pump, maintaining the balance between sodium (Na) and potassium (K) inside and outside heart muscle cells. This is essential to enable the rhythmic contraction and relaxation of the heart. Their research fed into a body of evidence demonstrating the significance of the sodium-potassium pump in heart failure [9-11], offering a new potential therapeutic avenue. Further research is underway to identify how best to target it.

Heart failure and arrhythmia

Heart failure is characterized by electrical instability, which not only makes the heart pump weaker, but can also lead to abnormal heart rhythms (arrhythmia). A large proportion of patients with heart failure suffer from severe arrhythmia, which is associated with the risk of hospitalization, worsening of heart failure, and sudden death. Several BHF-funded studies have investigated how arrhythmia develops in the context of heart failure.

Important contributions in this area have been made by BHF funded Professor Stuart Cobbe at the University of Glasgow, who developed a rabbit model of heart failure to investigate the electrophysiological changes associated with the condition [12]. Additionally, he helped develop pioneering optical mapping techniques for cardiac conduction in isolated hearts, allowing cardiologists to identify how heart failure disturbs the way the electrical impulses in the heart are routed.

BHF-funded Professor Mark Boyett, Dr Halina Dobrzynski and colleagues at the University of Manchester have highlighted the importance of direct changes in ion channel expression and regulation in the development of heart-failure induced arrhythmia[13]. BHF also funded Professor Andre G Ng and colleagues at the University of Leicester who have demonstrated extensive electrical, structural, and neuronal remodeling in a preclinical model of heart failure, which create the conditions necessary for the development of arrhythmias[14].

II. Mechanics of heart contraction

The components within the heart muscle cells responsible for enabling muscle contraction also play a role in sensing mechanical signals from their surroundings (mechanosensing). These components are now understood to be a central hub for controlling how the body responds to injuries and changes in the heart's structure (cardiac remodelling). Heart failure in its various forms is often due to problems with cardiac contractility and the consequences of mechanical overload.

BHF has funded several projects on this topic. Some studies looked directly at the sarcomere components (main contractile unit of muscle fibre) and their regulation. Work by Professors Metin Avkiran and Jonathan Kentish at King's College London contributed to our understanding of cardiac muscle regulation and its relevance to cardiovascular disease. The team investigated the role of protein kinase D (PKD) and highlighted its potential role in regulating the function of the heart's contractile apparatus[15].

BHF-funded research led by Dr Sam Boateng at the University of Reading aimed to understand the mechanisms behind impaired mechanosensing in cardiac muscle cells which contributes to the development of heart failure. They studied the muscle LIM protein, which plays a role in mechanosensing, and found that it

is regulated by cell contractility. The study also revealed that the loss of mechanical sensitivity contributes to heart failure, making it the first study to indicate that mechanosensing could be modified pharmacologically during the transition to heart failure[16].

III. Energetics of heart contraction

The pumping action of the heart is highly energetic. It requires the generation of ATP via metabolic pathways to provide the energy required for the contraction of cardiac muscle. Appropriate energy production and consumption is essential for maintaining the pumping action of the heart to ensure circulation of oxygen and nutrients throughout the body.

Heart failure is characterised by an imbalance in energy production and utilisation; therefore, it is strongly associated with defects in cardiac metabolism. Whether heart failure is caused by these defects, or whether these are the consequence of heart failure is highly debated. But the spiraling phenomenon of increased and dysfunctional metabolic demand and the detrimental consequences on the metabolic machinery are likely to be one of the most important factors that perpetuate heart failure. BHF has been at the forefront of funding research into cardiac metabolism.

Magnetic resonance spectroscopy (MRS) is a noninvasive diagnostic test that can provide insights into the biochemical processes within the body. As early as 1982, BHF supported MRS research at the University of Oxford led by BHF Professor George Radda and his group. This work allowed the systematic development of MRS and has provided fundamental new insights into the metabolic changes that occur in the diseased heart in heart failure[17].

Researchers in Oxford led by Professor Oliver Rider used MR spectroscopy to describe how the beating heart utilises different sources of energy, in particular glucose and fatty acids[18]. The team were able to show how the heart handles energy use at rest and during exercise[19]. This was followed by the discovery that a lack of available energy to heart muscle cells during exercise is a key mechanism of a form of heart failure in which the heart becomes abnormally stiff ('diastolic heart failure')[20]. These findings suggest that some forms of heart disease could be treated by targeting how the heart uses different sources of energy which is the focus of more recent BHF-funded work. In 2022, BHF funded Professor Rider to carry out a clinical trial looking at whether increasing substrate supply to the heart can be used as a therapeutic strategy in heart failure. The impact of BHF research into cardiovascular MRI is covered in detail in a separate thematic review[2].

The research of Stefan Neubauer, Professor of Cardiovascular Medicine and consultant at John Radcliffe Hospital has investigated energy metabolism in heart failure. His work has covered the full spectrum from discovery science to

[2] https://www.bhf.org.uk/impactofmri

translational and clinical studies. His research interests include the role of creatine kinase (CK) in cardiac metabolism, an enzyme that facilitates the conversion of creatine and ATP into ADP. Neubauer and his team have shown in mice that increased CK activity protects the heart muscle from damage following a heart attack and improves functional recovery. However, increasing CK in a model of chronic heart failure was not beneficial[21]. The team also produced the first evidence that low levels of the amino acid homoarginine impairs heart function and that homoarginine supplementation in mice improves how the heart contracts and relaxes in a model of chronic heart failure[22]. Supplementation with homoarginine is safe, cheap, and easily administered, and this study presented a promising approach for clinical translation[23].

b) Central and hormonal regulation of heart contraction

Several organs can influence the pumping action of the heart, including the brain, the adrenal glands, and the kidneys. Those systems are highly interlinked. Dysfunction in any of these systems can affect how well the heart is pumping blood throughout the body. BHF-funded research has contributed to generating knowledge of the various mechanisms involved in the regulation of heart contraction, how they are affected in the context of heart failure and how they are targeted by heart failure treatments.

I. The adrenaline/noradrenaline pathway

The central nervous system, and especially the sympathetic system, often referred to as 'fight or flight' system, plays an important role in the regulation of heart contraction. This is mainly controlled by the catecholamines, noradrenaline and adrenaline. The two neurotransmitters bind to receptors on heart cells, called adrenoreceptors, leading to increased heart rate and contractility. Since it was founded, BHF has funded research into the role of neurotransmitters in the development and progression of heart failure.

Drugs blocking the action of adrenaline and noradrenaline, called beta-blockers (e.g., propranolol), were developed in the 1950s to treat angina. Beta-blockers slow down the heart rate and reduce the force at which blood is pumped around the body. They were contraindicated for heart failure up to the late-1990's due to concerns that they would worsen cardiac contraction further. But researchers around the world have worked towards debunking that myth, including researchers funded by BHF.

Jack Shillingford, who later became BHF Professor of Cardiovascular Medicine and BHF's first Medical Director, was funded by the BHF in the 1970s to investigate the causes of the development of heart failure following a heart attack. Professor Shillingford and his team looked specifically into the role of adrenaline and noradrenaline; and together with Professor David Hearse, they were testing the effect of various drugs targeting the adrenaline/noradrenaline pathway on the isolated perfused heart. Following more research in this space,

including the landmark International Studies of Infarct Survival (ISIS) led by BHF Professor Peter Sleight in the 1980s, the positive impact on patient prognosis associated with beta-blockade after a heart attack was clearly demonstrated. Prescription of beta-blockers after a heart attack has now become standard practice worldwide to limit the development of heart failure.

Following this, scientists and clinicians started to investigate the action of beta-blockers on heart cells and heart function and test the use of beta-blockers in the treatment of heart failure. This included BHF funded researchers Professor Robin Shanks and Dr Kofi Ekue in Belfast[24]; Professor John Muir in Cardiff[25]; Professor AM Barrett in Leeds[26]; BHF Professor Philip Poole-Wilson and Professor Sian Harding in London. This research led to the demonstration in several large clinical trials of the improved survival and reduced risk of hospital admission associated with beta blockers in patients with chronic heart failure. Beta blockers are now one of the "four pillars" of the pharmacological treatment of heart failure, their use being recommended in all national and international guidelines[2, 27, 28].

Other therapeutic avenues targeting the catecholamine pathway are still being explored by BHF-funded researchers. Intimately related to beta-adrenergic receptors (βARs) is the physiology and pharmacology of cAMP signalling, a critical pathway that mediates the cellular response to various extracellular signals, including catecholamines via βARs. BHF has been funding Professor Julia Gorelik at Imperial College London and Professor Manuela Zaccolo at the University of Oxford who are looking in detail at this pathway in the context of heart failure. Both teams have developed novel imaging techniques to study local compartmentalisation of cAMP[29, 30].

Professor Zaccolo and colleagues have found that heart cells function correctly only if multiple cAMP-related signals are generated simultaneously, and each signal is located within an extremely small space within the cell. Each minuscule signal is different and responsible for a specific effect[29].

Professor Gorelik and colleague's research have shed light on the structural remodelling happening during the development of heart failure following a heart attack, and how it impacts βAR-cAMP signalling at a local level[31].

Both groups' research will give further insight about how cAMP signals are generated, what function each of them regulates, how they work in a coordinated manner, and how these localised signals change in the diseased heart. Their research could inform a 'precision medicine' approach by targeting specific pools of cAMP within cells, to correct individual functions in heart failure.

II. The heart-kidney axis

The kidney plays an important role in the regulation of heart contraction and in the development of heart failure. The renin – angiotensin – aldosterone system (RAAS), primarily controlled by the kidneys, is a complex hormonal system that is essential for the regulation of heart blood pressure and fluid balance in the body.

Both blood pressure and blood volume (controlled by fluid balance) can affect the contraction of the heart.

Several BHF funded researchers have contributed towards better understanding how RAAS controls blood pressure and is involved in the development of hypertension and chronic renal failure, two conditions that can lead to the development of heart failure. For example in the 1970s, BHF funded Dr MA Waite who developed assays to measure the levels of renin and angiotensin I and II (key components of RAAS) in the blood[32, 33]. They found a six-fold increase of these proteins in the blood samples of patients with chronic renal failure and hypertension. They also discovered that levels fall after bilateral nephrectomy (the removal of both kidneys), with the extent of the decrease related to a reduction in blood pressure[34]. At the time, the relationship between hypertension, chronic kidney disease and heart failure started to emerge. However, the mechanisms of increased blood pressure in chronic renal failure were not fully established. The findings from Waite et al. suggested an involvement of the renin-angiotensin system, adding to a body of evidence that targeting this pathway could help treat both hypertension and heart failure.

Today, several drugs used to treat heart failure are targeting the heart-kidney axis and RAAS specifically, including:

- ACE inhibitors, they prevent an enzyme called angiotensin-converting enzyme (ACE) in the body from producing angiotensin II which can narrow blood vessels and increase blood pressure.
- Angiotensin receptor blockers (ARBs), they reduce the action of angiotensin II by blocking the receptors angiotensin II acts on, which are found in the heart, blood vessels and kidneys.
- Diuretics, they help the kidneys remove salt and water through urine, lowering blood volume and pressure. Therefore, preserving heart function.

Recent clinical trials have also found that SGLT2 inhibitors can be used in the treatment of heart failure. SGLT2 inhibitors are oral glucose-lowering agents used in the treatment of type 2 diabetes. They also have a diuretic effect and are therefore relevant to heart failure. SGLT2 inhibitors have been shown to improve prognosis for patients with chronic heart failure; importantly, this benefit is seen for all types of heart failure, with benefit in HFrEF, HFmrEF and HFpEF. However, it is not yet known how exactly SGLT2 inhibitors improve heart failure prognosis. BHF Professor Sven Plein and colleagues at the University of Leeds have found that the SGLT2 inhibitor empagliflozin could enhance the energetics and function of the heart[35]. Finding out more about how SGLT2 inhibitors protect the heart could lead to novel therapeutic avenues for the development of new heart failure treatments[3].

[3] https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2021/june/drug-used-to-reduce-blood-sugar-levels-in-diabetic-patients-could-also-benefit-hearts

c) Discovering new pathways

Heart failure is a complex disease: the arrays of compensatory and adaptive mechanisms overlap with the consequences of the initial injury, the effects of the diverse treatments and often, especially in older patients, associated diseases. This results in a pleiotropic gene expression response (one gene influences multiple traits), often reverting to a foetal pattern with a myriad of changes in the expression of regulatory genes, transcription factors, and signalling pathways. The advent of –omics techniques has resulted in an even more complex picture, with the consequence of a very difficult interpretation and application of the results. The BHF-funded projects in this area reflect this complexity.

From MURF2 to RK1, from calcineurin to Pak3, many signalling pathways have been investigated and found to be altered in heart failure. Of particular interest was the altered expression of the transcription factor RUNX1, examined by the Loughrey laboratory from Glasgow University. Using RUNX1- deficient mice, this group showed the central role of this factor in remodelling and expression patten and phosphorylation of key calcium regulation pathways[36].

Researchers are beginning to understand how natural variations in genes might protect against heart diseases linked to ageing, such as heart failure. BHF has been funding Professor Paolo Madeddu at the University of Bristol who is investigating the potential of gene therapy to reduce the damage caused by aging in the heart. Professor Madeddu and the MultiMedica Group in Italy have discovered that a naturally occurring variant of the BPIFB4 gene, which is more common in people who live to 95 or more, could help keep the heart young. They found that a single administration of the mutant anti-ageing gene halted the decay of heart function in middle age mice[37]. When given to elderly mice, whose hearts exhibit the same alterations observed in elderly patients, the gene rewound the heart's biological clock age by the human equivalent of more than ten years. Now, the team is exploring an alternative approach: instead of injecting the gene, they are investigating whether providing the protein directly to mice (orally) can achieve similar results. This practical method could pave the way for future interventions to keep ageing hearts healthy.

d) Role of the blood vessels

Cardiac microvascular dysfunction is a condition where heart muscle cells do not receive enough oxygen due to abnormalities in the structure and function of the small blood vessels within the heart muscle. This can lead to a condition known as myocardial ischemia, which refers to inadequate oxygen supply to the heart muscle. Over time this can contribute to the development of heart failure.

The limited understanding of the relationship between vasculature and myocardial remodelling in heart failure has triggered significant interest from several research groups and BHF has funded a very substantial amount of work on this subject.

Professor Adrian Hobbs at Queen Mary University London has studied the role of C-type natriuretic peptide (CNP) and discovered that it is released from the endothelium and helps protect blood vessels from disease[38]. Subsequent BHF-funded studies have aimed at further understanding its role in cardiovascular disease. The team discovered that CNP protects the heart in cardiovascular disease including heart failure and that loss of CNP can make heart failure more severe. They also identified the receptor which is responsible for mediating the beneficial actions of CNP. Their work implies that CNP-targeted drugs could be of therapeutic benefit in cardiovascular disease[39]. Professor Hobbs has since been working on developing new molecules that activate the CNP receptor, with an aim to take forward to animal studies and clinical trials.

e) Cardiac remodelling

Cardiac remodelling refers to the structural and functional changes that occur in the heart in response to stressors, such as heart attack or heart valve problems. These changes can be adaptive initially, but in the context of heart failure, they become maladaptive and contribute to the progression of the disease.

The Shah laboratory at King's College London, supported by BHF, has invested much of its work on the regulation of NADPH in heart failure and its importance in remodelling[40]. Ajay Shah is currently BHF Professor of Cardiology. Professor Shah's research has focused on the role of the enzymes NADPH oxidases (NOXs). NOXs produce reactive oxygen species (ROS), or free radicals, which are considered bad for the heart. The team found that two types of NOX - NOX2 and NOX4 - are more active in heart failure. NOX2 was shown to be harmful as it promotes muscle thickening and scarring[41]. Unexpectedly the researchers noticed that NOX4 can benefit the overworked heart by increasing the blood supply to the heart muscle and improving antioxidant defense pathways[42]. Professor Shah's team are now investigating whether they can use this knowledge about NOX4 to boost the heart's own adaptive remodeling processes, which could lead to a new way to prevent heart failure.

Many other BHF-funded groups are studying cardiac remodelling. For example, Dr Chris Watson at Queen's University Belfast investigated the role of Tetranectin in cardiac remodelling and its utility as a heart failure biomarker[43]. At Imperial College London, Dr Javier Barallobre Barreiro is investigating the contribution of ADAMTS proteases in extracellular matrix remodelling.

f) Apoptosis and heart failure

Apoptosis (programmed cell death) is a hallmark characteristic of cardiovascular disease, including heart failure. BHF Professor Kinya Otsu and colleagues at King's College London have studied how heart cells die during heart failure, and the chemical signals involved. The group have investigated the role that mitochondrial DNA has in cell damage and cell death (mitophagy)[44]. In addition, the role of cytokine mRNA degradation in the pathophysiology of heart failure has also been investigated by this group. Using transgenic mice and adeno-associated virus gene transfection, they have shown that Regnase-1, an RNAse responsible for the degradation of proinflammatory cytokine mRNAs in immune cells, can protect from inflammation and prevent cell death in pressure overload[45].

Research by Dr Gavin Richardson at Newcastle University has focussed on heart cell ageing, and how this contributes to heart disease, including heart failure. They found that after a heart attack, senescent cells, also known as zombie cells, build up in the heart and prevent recovery[46]. They also found that removing these zombie cells, by treating mice with navitoclax improved recovery of the heart muscle[47]. The Newcastle team, in collaboration with researchers at the Mayo Clinic in the US, Queen's University Belfast and INSERM in France, hope that this drug could be used within the next decade to help people recover from a heart attack. Dr Richardson's current research is investigating whether the removal of senescent cells helps to reduce damage and restore heart function following reperfusion injury in mice. The findings could pave the way towards new treatments to help the heart recover following heart attack and to reduce the risk of heart failure. Future work by the team will investigate the role of anti-cancer drugs in producing senescent cells which can cause heart failure.

3) Developing new technology

a) Imaging

Imaging technology is instrumental in heart failure, serving as a diagnostic as well as a prognostic tool. One of the most common types of heart scan is an echocardiogram, which uses ultrasound to check the structure of the heart and surrounding blood vessels. Echocardiography plays an important role in the diagnosis and management of patients with heart failure. BHF was involved from the early days of echocardiography, funding a programme in the 1980s which provided ultrasound scanners for several hospitals in the UK for clinical and research use. BHF also helped to make echocardiograms more widely available,

by giving grants for portable echo machines that could be used outside of hospitals, and by enabling the training of specialist technicians. Since then, BHF has been funding research using advanced technologies to improve and refine the use of echocardiography for diagnosing and managing heart failure. For example, in 2023, BHF funded a project led by Professor Darrel Francis at Imperial College London which aims to integrate artificial intelligence into echocardiography to speed up image analysis.

Many BHF-funded advances in imaging technologies have been used in the field of heart failure. This includes magnetic resonance imaging (MRI), a non-invasive imaging technology that produces highly detailed images of the heart and blood vessels and accurate information on the anatomy and function of the cardiovascular system. The impact of BHF research into cardiovascular MRI is covered in detail in a separate thematic review[4]. Dr Andrew Flett at the University of Southampton is currently leading the BRITISH trial which is using MRI to test whether heart scarring can indicate when people with heart failure should receive an ICD. The trial will focus on patients with heart failure due to non-ischemic cardiomyopathy (NICM). NICM is when heart failure is due to a condition not caused by narrowing in the coronary arteries. The results of BRITISH could provide vital information to either support or disprove whether heart scarring can be used to improve how people with NICM are selected for an ICD, helping to ensure that patients receive the best possible, evidence-based care.

Studies have shown that analysing arterial waves could help distinguish between two types of heart failure - systolic heart failure where the heart does not contract adequately, and diastolic heart failure where the heart does not relax fully. Until now, methods for measuring arterial wave intensities were too invasive, inaccurate or expensive for routine use. Research part funded by BHF and led by Professor Peter Weinberg at Imperial College London has developed an easy-to-use, non-invasive and relatively low-cost method called ArterioWave[5][48, 49]. ArterioWave senses changes in wave intensity continuously over the cardiac cycle from spatially and temporally coincident measurements of blood velocity and arterial diameter. The translation of this technology to the clinic could allow GPs, sonographers and nurses, as well as specialists, to offer patients earlier, easier, and more frequent evaluation of heart function in the community and on the ward.

[4] https://www.bhf.org.uk/impactofmri
[5] https://imperial.tech/our-technologies/arteriowave-simple-ultrasound-based-diagnosis-and-monitoring-of-heart-failure/

I. Artificial Intelligence in imaging

Artificial Intelligence (AI) refers to the spectrum of computer science that focuses on simulating human cognitive processes. BHF funded a study led by Professor Declan O'Regan and colleagues at Imperial College London that investigated whether AI could make better predictions about heart failure patients. Professor O'Regan and colleagues developed a deep learning cardiac motion analysis program called 4D survival. The program automatically interpreted thousands of heart scans and built a detailed three – dimensional model of the heart, so that the computer could learn to recognise the earliest and most important signs of heart failure.

The team used 4D survival to predict the prognosis for 302 patients[50]. Results from the trial showed that the program outperformed doctors and was able to correctly predict a patient's prognosis 75% of the time, confirming that a computer is able make better predictions about patients' health compared to the best available methods that doctors currently have.

In response to these promising results, the team filed for a patent for this technology and received follow-on funding from the National Institute for Health Research (NIHR).

Professor O'Regan has also used AI to analyse MRI scans of over 18,000 people from UK Biobank and showed that people with a more complex network of trabeculae - 'strand-like' muscle structures in the heart - had an increased capacity to pump blood, which may offer protection against the development of heart failure[51][6].

b) Regenerating the heart

Currently, a heart transplant is one option for end-stage heart failure. However, there is a severe shortage of donor hearts, and people with severe illness may not be able to withstand the surgery. Therefore, transplantation is only possible in a small number of cases. An exciting field of research has emerged, called regenerative medicine, in which researchers around the world are searching for ways to repair or regenerate damaged heart tissue. The prospect of being able to mend damaged heart muscle brings hope that one day, a heart transplant may no longer be necessary for any patient with heart failure.

In 1973 the BHF funded its first regenerative medicine research project led by Professor Donald Longmore at the National Heart Hospital in London, to

[6] https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2020/august/structures-inside-heart-reveal-heart-failure-risk

investigate how stem cells could help the repair of heart tissue damaged by a heart attack. Since 2013, BHF has increased its investment in regenerative research, establishing three BHF Centres of Regenerative Medicine, supporting a structured network of high-level groups in several UK universities. From stem cells to drugs, biomaterials to gene therapy, BHF-funded researchers have been looking into a range of therapeutic options to repair and/or regenerate damaged heart tissue. Examples include Professor Mauro Giacca's work at King's College London which is investigating injectable gene therapies that could promote heart repair after a heart attack and prevent heart failure[52]. Professor Andrew Baker at the University of Edinburgh is developing new stem cell therapies to regrow lost or damaged blood vessels, particularly after a heart attack. And Professor Paul Riley at the University of Oxford has demonstrated in mice that adult heart cells can be stimulated chemically to repair heart damage[53].

In 2024, BHF joined forces with the Medical Research Council (MRC) to launch a new gene therapy research centre focussing on heart repair and regeneration[7]. The MRC/BHF Centre of Research Excellence in Advanced Cardiac Therapies will be led by Professor Mauro Giacca at King's College London, BHF Professor Andrew Baker at the University of Edinburgh, and BHF Professor Paul Riley at the University of Oxford. The centre aims to develop the first therapies to stimulate heart repair and regeneration in patients following a heart attack and in those with established heart failure.

BHF investment in this area has laid a robust foundation and unveiled promising therapeutic avenues. While the path to deliver substantial patient benefits is ongoing, the progress made so far is encouraging.

I. Stem cell patches

Since 2010, BHF has funded Professor Sanjay Sinha's team at the University of Cambridge to develop a 'heart healing patch' using stem cells. By using stem cells and giving them a specific mixture of proteins called growth factors, Professor Sinha's team have been able to stimulate the cells into becoming heart tissue[54]. The team aims to graft the tissue onto damaged areas of the heart to help repair it. The technology behind the heart healing patch has been successful in rats. Professor Sinha's team hope to start the first tests in people, in the next five years.

Researchers at Imperial College London, led by Professor Sian Harding have developed a 3D 'beating' stem cell patch. The patch, designed to support and stimulate heart muscle repair, was developed in response to the ineffectiveness of direct stem cell injections into the heart. By collaborating with bioengineers,

[7] https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2024/december/transformational-new-gene-therapy-research-centre-launched

including Professor Dame Molly Stevens, the team used auxetic patterning[55] to increase biocompatibility and successfully tested the patches on rabbits in 2019[56], showing improved cardiac function and reduced scar size[57]. Auxetic patterns are structures or materials that, when stretched, become thicker perpendicular to the force. Future steps will be to use these results to design clinical trials.

Both stem cell research projects were supported by BHF Centres of Regenerative Medicine, with Professor Sinha being part of the centre at Cambridge, and Professor Harding at Imperial (Professor Harding was Director of the Imperial College BHF Centre of Regenerative medicine until her retirement in 2021).

Stem cell therapy shows promise for the treatment of heart failure. However, there are hurdles to overcome before it can become a routine and successful treatment. With BHF support, Professor Ken Suzuki has developed a new type of stem cell therapy called AMSC-dressing therapy[58]. The type of stem cells used in this therapy, and the way they are introduced to the heart, have significant advantages over other methods. In this treatment, a biodegradable patch that contains stem cells is placed on the outside of the heart. In rats, this promotes some repair of heart muscle damaged by a heart attack. Professor Suzuki and his team will now investigate how effective AMSC-dressing therapy is at treating heart failure caused by different diseases. Their goal is to develop a non-surgical method to transfer stem cells to the heart and understand how these cells repair damaged muscle. If successful, this research could lead to an effective stem cell therapy being widely adopted in clinical practice.

II. Gene therapy

Another area of interest in regenerative medicine is gene therapy, addressing underlying genetic factors and promoting heart tissue regeneration. Professor Mauro Giacca and his BHF-funded team at King's College London are investigating the potential of injectable gene therapies to improve heart muscle function following a heart attack. The team discovered three new proteins that can be injected directly into the heart immediately after a heart attack, which could prevent heart failure. The three proteins Chrdl1, Fam3c and Fam3b were discovered using the protein 'search engine' FunSel[59]. After preclinical testing, the team plan to take the innovative treatment to patient clinical in the next two years. In 2022, Professor Giacca founded the spin-out company Forcefield Therapeutics[8], backed by leading FTSE 250 healthcare company Syncona, with the aim of accelerating clinical translation.

[8] https://forcefieldtx.com/

4) Influencing clinical practice

BHF-funded research has influenced the way heart failure patients are managed, from creating a simple test to help diagnose the condition, to finding the best treatments to improve survival and quality of life.

a) Diagnosing heart failure

I. A blood test for heart failure diagnosis

Professor Allan Struthers and BHF Professor Phillip Poole-Wilson, were amongst a team of doctors who transformed the early diagnosis of heart failure. Diagnosing heart failure early is essential so that patients can be started on the right treatment. However, prior to the 1990's, diagnosing heart failure was challenging, as many of its symptoms such as breathlessness and fatigue can be caused by several other conditions.

In 1997, Allan Struthers and Phillip Poole-Wilson discovered that a simple blood test could allow for an earlier diagnosis of heart failure[60]. The test measures levels of B-type natriuretic peptide (BNP) in the blood. Research found higher concentrations of BNP in the blood of heart failure patients, meaning those with low readings were unlikely to have heart failure, and those with higher readings needed investigation. In 2004, BHF funded Professor John McMurray to investigate whether BNP measurement to guide medical treatment could improve heart failure outcomes. Prof McMurray later contributed to the evidence that BNP testing is cost-effective[61]. In 2010, national guidelines for doctors included the BNP test as part of the gold standard for heart failure diagnosis. By 2016, MPs were urging all GP practices to adopt the test, as it allows them to identify at risk patients and make referrals faster for tests such as echocardiograms, which can confirm if symptoms such as breathlessness might be due to heart failure. Faster referrals allow for earlier diagnoses, meaning patients can receive essential care and treatment as soon as possible.

b) Treating heart failure

There isn't a cure for heart failure, however, available treatments can help patients manage symptoms and improve their quality of life. Treatments for heart failure include heart surgery, medication, and pacemakers or ICDs. BHF-funded research has influenced how patients with heart failure are treated today.

I. Heart transplantation

The primary treatment option for end-stage heart failure is heart transplant and in the present day, approximately 200 heart transplants are performed annually in the UK. Since its inception, BHF has provided key funding into pioneering heart transplant research. In 1968, following 5 years of BHF-funded research into heart transplant techniques, heart surgeon Donald Ross performed the UK's first and the World's 10th heart transplant[62].

A key challenge of heart transplantation is rejection of the donor heart. In 1985, BHF funded the work of BHF Professor Sir Magdi Yacoub at Imperial College London which focused on understanding rejection mechanisms and tested immunosuppressant regimens to reduce rejection risks[63]. More recently, BHF has funded the work of Professor Federica Marelli-Berg and colleagues at Queen Mary University of London, who are using an innovative approach to tackle heart transplant rejection. At Kings College London, Professor Giovanna Lombardi has studied the role of a subset of immune cells called T regulatory cells that can suppress the immune response[64]. BHF has produced a separate thematic review on cardiac surgery, which covers the impact of BHF research on heart transplantation in detail[9].

II. Medication

Beta-blockers

BHF-funded studies have been integral in defining beta-adrenoceptor (βAR)/beta-blocker mechanisms in heart cells and in heart failure patients and contributed to the successful translation of those benefits into clinical practice. In the 1980s, BHF Professor Peter Sleight, from the University of Oxford, kick-started the International Studies of Infarct Survival (ISIS). The first trial, ISIS 1, showed that beta-blockers significantly improved heart attack recovery[65]. Giving patients these drugs after a heart attack has now become standard practice worldwide to limit the development of heart failure.

Other pioneers include BHF Professor Phillip Poole-Wilson and colleagues at

[9] https://www.bhf.org.uk/what-we-do/our-research/research-successes/our-research-impact-reports/our-cardiac-surgery-research-report

Imperial and the Royal Brompton Hospital, who designed and led pioneering randomised clinical trials which contributed towards defining the use of beta-blockers in heart failure[66, 67]. In the last 30 years, the introduction of beta-blockers as routine therapy has been one of the most significant advances in the treatment of heart failure.

Many people stop taking beta-blockers, due to concerns around side-effects. Dr Graham Cole at Imperial College London is leading a study to understand why some heart failure patients stop taking their medication, where only minimal side effects were reported in trials. This could help people living with heart failure to better understand that their medicine is safe and to encourage them to continue taking their lifesaving treatment.

ACE inhibitors

Heart failure can develop after a heart attack if the heart muscle is extensively damaged. BHF research has shown that treatments given immediately after a heart attack can help limit this long-term damage.

BHF-funded Professor Stephen Ball and colleagues at the University of Leeds led a ground-breaking clinical trial in 1993 which revolutionised heart attack treatment. The study found that ACE inhibitors (angiotensin-converting enzyme inhibitors), given to patients with signs of heart failure in the days after a heart attack, could save lives[68]. ACE-inhibitors reduce the activity of angiotensin-converting enzyme (ACE), which is responsible for hormones that help control blood pressure. It has a powerful narrowing effect on blood vessels, which increases blood pressure. ACE inhibitors inhibit or limit this enzyme, causing blood vessels to relax and widen, in turn lowering blood pressure improving blood flow to the heart. These drugs also have important, positive effects on remodelling of the heart after a heart attack and in other types of chronic heart failure, leading to positive effects on patient survival and well-being.

The Acute Infarct Ramipril Efficacy Study, more commonly known as the AIRE study found that for every 18 patients treated in the trial, they were able to prevent the death of 1 patient. Additionally, the trial confirmed that ACE inhibitors gave patients an increased chance of recovery with higher quality of life. The results of the trial provided compelling evidence for the use of these drugs in treatments for those with diagnosed heart failure after a heart attack, and has influenced clinical practice worldwide. A study examining 3-year mortality trends among UK heart attack survivors who had survived for 3 months revealed a significant increase in ACE inhibitor usage, rising from 11% to 71% between 1991 and 2002. Concurrently, mortality during this timeframe decreased by 28%[69].

The results also inspired future studies. Most notably is the BHF-funded study led by Professor Allan Struthers and colleagues at the University of Dundee. Their research showed that adding the diuretic (water tablet) spironolactone to ACE inhibitors increased the beneficial effect. These results were later confirmed in a

large international clinical trial that revealed spironolactone reduced death rates in people with heart failure by 30%[70].

BHF is currently funding a trial led by Professor Patrick Mark at the University of Glasgow to investigate whether spironolactone can help reduce heart-related complications in people with kidney failure. People with kidney failure who need dialysis are at high risk of heart failure and heart-related death. There are currently no proven treatments to reduce this risk, as previous trials of heart failure treatments have tended to exclude people with kidney problems. If the trial finds that spironolactone is beneficial and safe, it could lead to this drug being routinely prescribed to people on dialysis for kidney failure.

Iron supplementation

BHF's IRONMAN study was successful in proving the long-term benefit regular iron infusions had on patients with heart failure[71].

Patients with heart failure often have low iron levels in their body, even in the absence of anaemia. Low iron levels are associated with more severe symptoms such as limited exercise capacity and an increased risk of being admitted to hospital. While short-term studies have shown the positive impact of iron injections on quality of life and exercise capacity, the long-term impact of iron supplementation on heart failure was unclear. Professor Paula Kalra and Trial Director Ian Ford set out to answer this question through the BHF-funded IRONMAN study. The scope of the study was sizable, with approximately 70 hospitals and 1137 people with heart failure and low iron levels participating. Participants were randomly assigned to either the pathway of standard heart failure treatment or the pathway of intravenous iron injections alongside their normal heart failure treatment. The study found that the risk of being hospitalised for heart failure or dying from a heart related cause was 18% lower in the group that received iron transfusions. Patients that received iron transfusions also reported a better quality of life after just 4 months. The study has shown that a straightforward and inexpensive treatment is a safe and effective way to reduce the risk of hospitalisation for heart failure. In 2023, the European Society of Cardiology (ESC) heart failure guidelines were updated to recommend intravenous iron to reduce symptoms and improve quality of life for heart failure patients with iron deficiency[72].

Discontinuing heart failure medication in dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a disease where the heart muscle becomes 'dilated', or stretched. As a result, the heart becomes weak which can lead to heart failure. Patients with DCM and heart failure often take multiple types of medication to improve heart function. And in some people, symptoms can resolve completely. This led to patients questioning whether they needed to continue taking their medication. In particular, young women are often keen to stop

treatment before trying to become pregnant. In 2016, a BHF-funded study led by Professor Sanjay Prasad at the Royal Brompton Hospital found that people with DCM should not stop taking heart failure medications[73]. The TRED-HF trial provided invaluable evidence to back-up long term prescription of medication in people with DCM, even if their heart failure seems to have recovered. In 2023, BHF funded a follow up trial TRED-HF2, which is investigating whether patients with DCM in remission can safely reduce the number of medications they are taking. They believe that beta-blockers may be the most important drug to maintain remission, and some other drugs are no longer required.

III. ICDs and pacemakers

Patients with heart failure often have electronic devices, either pacemakers or implantable cardioverter defibrillators (ICDs), to help manage their condition and mitigate the risk of any adverse effects such as arrythmias. A pacemaker is a small electrical device that is implanted into the chest. The purpose of a pacemaker is to artificially take over the role of the sinus node if the heart is beating too slowly or missing beats. Some pacemakers can also help the chambers of the heart to beat in sync.

An ICD is a defibrillator that shocks and kickstarts the heart if it goes into a life-threatening rhythm or cardiac arrest. The device is placed just under the collar bone, with thin wires connected to the heart that monitors heart rate and rhythm. An ICD can deliver three or more possible treatments if it identifies an abnormal heart rhythm.

- Pacing – a series of low-voltage electrical impulses (paced beats) at a fast rate to try and correct the heart rhythm.
- Cardioversion – one or more small electric shocks to try and restore the heart to a normal rhythm.
- Defibrillation – one or more larger electric shocks to try and restore the heart, which has in effect stopped, to a normal rhythm.

BHF has funded pioneering research that has explored various new ways in which ICD's and pacemakers can be used in the treatment of heart failure.

Developing a new pacemaker therapy to improve heart failure symptoms

In 2016, BHF funded a clinical trial led by Dr Zachary Whinnett at Imperial College London to discover whether a new type of pacemaker therapy can improve symptoms in heart failure.

Some heart failure patients suffer from left bundle branch block (LBBB). In these patients, their right and left sides of their heart do not beat concurrently, signifying that their hearts electrical conduction system is not working as it should be. The common treatment for LBBB is a pacemaker therapy called Cardiac Resynchronisation Therapy (CRT). CRT works similarly to a normal pacemaker, but also sends small electrical impulses to the left and right sides of the heart to help them beat together. Although effective, CRT had only been shown to be beneficial in patients who have LBBB. It was unclear whether CRT could help heart failure patients with PR interval prolongation, which causes abnormal delays between the heart's upper and lower chambers during each heartbeat.

A significant drawback of pacemaker therapy is they do not activate the heart through its usual conduction system which over time, which can lead to a further impaired heart function and an increase in heart failure symptoms. His-bundle pacing therapy was developed as an alternative pacing approach that delivers electrical signals directly to the hearts own conduction system.

Dr Zachary Whinnett's trial 'His Optimised Pacing Evaluated for Heart Failure' (HOPE-HF) aimed to find out whether an alternative pacing technique, alongside a method for identifying the best pacemaker settings, could help improve symptoms for people with heart failure and PR prolongation. The study found that His pacing did not improve participants ability to exercise. However, His pacing was linked to better quality of life and improved symptoms, measured using the 'Minnesota Living with Heart Failure Questionnaire.' 76% of participants reported that they preferred having His pacing on[74]. HOPE-HF highlighted that His pacing is both safe and feasible for heart failure and PR prolongation patients, providing a clear basis and strong argument for a future longer-term trial.

BHF is currently funding another trial led by Dr Whinnett which is testing a new pacemaker method for treating slow heart rate (bradycardia). The standard way of pacing can be lifesaving, but because it doesn't activate the heart through its normal electrical conduction system it can lead to heart failure. The PROTECT-HF trial aims to definitively test whether physiological pacing can reduce heart failure and death in the longer term compared to standard pacing.

Personalising pacemakers

In 2021, BHF-funded researchers at the University of Leeds started investigating how people living with heart failure, specifically HFrEF, can benefit from personalised pacemaker programming. Pacemakers are programmed using a default algorithm to increase the heart rate during exercise. However, the Leeds team, led by Professor Klaus Witte, have shown that this 'one size fits all' algorithm does not always improve a person's ability to exercise. The team will now test whether using personalised heart rate settings could improve the heart rate during exercise. If successful, the personalised programme could inform the benefits of personalised management of heart failure patients and provide information to guide the development of the next phase of the clinical trial.

Should Patients Receive ICDs Earlier?

BHF-funded researchers at King's College London conducted a study which proved that heart failure patients should not have to wait until after having a stent fitted to receive a potentially lifesaving ICD. Coronary heart disease is the leading cause of heart failure. It develops when the blood vessels supplying the heart become narrowed. Doctors insert stents to open any blocked arteries in people with this condition and will wait 90 days to see if they have an elevated risk of life-threatening heart arrythmias before considering giving them an ICD.

Professor Divika Perera led a multicentre trial involving 700 heart failure patients from 40 centres across the UK[75]. All patients in the trial received optimal medical therapy which included heart failure medication, as well as pacemakers and ICDs. Half of the patients were assigned to also have stents fitted to open their narrowed arteries. The study found that stents were not shown to improve the heart's ability to pump, or reduce the risk of life-threatening arrythmias, cardiac arrest or death. These results confirmed that high risk patients should be able to receive ICDs earlier. This could influence heart failure guidelines in the UK, Europe and internationally.

II. Other approaches

Professor Gerry McCann at the University of Leicester is running a trial which hopes to answer the question 'does losing weight offer hope to people with heart failure?'. The trial focuses on patients with HFpEF, where limited treatments are available. Researchers have discovered that if HFpEF patients with obesity and diabetes lose weight, their exercise capacity improves and changes in their heart and blood vessels are reversed. In this project, Professor McCann and team will confirm these findings in a larger, multi-ethnic group of patients with established HFpEF using a commercially available diet plan.

c) Heart failure care and management

I. Improving heart failure care at home

BHF has developed and tested new ways of delivering care for heart failure patients, including at home, to improve lives and relieve the pressure that heart failure is putting on the NHS. Between 2004 and 2007, BHF evaluated the feasibility and effectiveness of a home-based heart failure programme led by heart failure specialist nurses. With support from the Big Lottery Fund, BHF funded 76 nurses in 26 NHS primary care organisations in England who saw approximately 15,000 patients. This programme led to a 35% reduction in

hospital admissions, and significant cost savings[10]. Thanks to this work, heart failure specialist nurse services are now well-established in many areas of the UK.

In 2011, BHF also supported heart failure specialist nurses to help give patients intravenous diuretics at home. The pilot showed that 100% of patients and 93% of family members preferred home-based treatment to hospital admissions, and that intravenous diuretics were safe and cost effective when used in a home setting[11]. The pilot has been adopted by NICE guidance as a 'Quality and Productivity: Proven Case Study' (QIPP) demonstrating how this programme delivers best practice. A number of NHS sites have since adopted the model.

II. Improving end-of-life care for heart failure patients

It's vital that people with advanced heart failure get the best quality care in the last stages of their life. Sadly, this is not always the case and people with heart failure are less likely than those with cancer to be offered specialist palliative care. In 2011, BHF partnered with Marie Curie and NHS Greater Glasgow and Clyde to improve the quality of palliative and end of life care for patients in the advanced stages of heart failure. The programme, Caring Together[12], piloted new integrated care models in Greater Glasgow and Clyde covering a population of 1.2 million people across a diverse geographical area. An evaluation of the project revealed that the programme improved symptoms and quality of life for people with advanced heart failure, provided individual patient planning, and reduced hospital admissions and healthcare costs.

III. Hope for Hearts Fund

In 2019, BHF launched a £1million funding scheme to transform the way heart failure services are delivered in the UK. The 'Hope for Hearts Fund' encouraged innovators from all sectors to partner with heart failure specialists and patients to help develop and implement new ideas for old problems. The hope was that projects would transform how people with heart failure experience care, use technology to improve the way services are designed and delivered, and

[10] https://www.bhf.org.uk/for-professionals/healthcare-professionals/innovation-in-care/heart-failure-specialist-nurses
[11] https://www.bhf.org.uk/for-professionals/healthcare-professionals/innovation-in-care/intravenous-diuretics-in-the-community
[12] https://www.mariecurie.org.uk/professionals/working-in-partnership/caring-together

introduce simple changes that could lead to huge impact. The following projects were funded through this scheme.

Automating MRI for better patient care

Cardiac function can be measured using cardiac MRI , a process that can be lengthy, requiring around 60 minutes for a basic examination. Once the images have been captured, they need expert analysis by a clinical expert. This expertise is rare, expensive, and variable. The inconsistency can potentially introduce errors in clinical-decision making, which can have profound effects on patients. To address these challenges, BHF-funded research led by Dr Rhodri Davies and Professor James Moon at University College London used AI to speed up the acquisition of cardiac MRI and automate image analysis. The initiative, supported by the Hope for Hearts Fund, successfully reduced the MRI scan duration from 36 minutes to 23 minutes. Not only were more patients able to be scanned per day, but there was also a better patient experience – MRI scans can be uncomfortable for patients so shorter scans would improve their experience. Other benefits included quicker reporting times (from 21 to 10 minutes) and increased precision in scan reporting. The AI has been rolled out to 5 centres in the UK and is also being used in Italy and the USA.

Improving patient access to MRI

Many patients living with heart failure have a pacemaker or ICD fitted to help manage their condition. The powerful magnets in an MRI scanner can cause interference on cardiac devices stopping them from working properly. Because of this, many heart failure patients face difficulties accessing MRI scans, leading to delays in the diagnosis and treatment of conditions that rely on MRI, such as cancer. With BHF funding, Dr Anish Bhuva and team at Bart's Health Trust and University College London developed a suite of resources called 'MRI MyPacemaker[13]' to improve referral and access to MRI for this underserved patient cohort. The team collaborated with seven professional societies and three patient charities to develop guidelines, supportive tools, and educational resources for clinicians and patients. The team also created an online referrals management platform to simplify the referral process so that any MRI or Cardiology department can offer the scans. The platform was deployed in three services with an MRI provision for over 500 patients. The new platform allowed referrers to make referrals within 7 minutes. Previously 25% of referrals took over an hour. The resources have been included in recommendation papers[76, 77] and the team at Barts won the BMJ Diagnostic Team of the Year in 2018 for their work on this project.

[13] https://mrimypacemaker.com/

Improving access to cardiac rehabilitation

Research funded by BHF and others has demonstrated that cardiac rehabilitation (CR) improves the day-to-day life of people with heart failure. However, only a minority of heart failure patients are referred to CR, which was often only offered to heart failure patients that had also suffered a heart attack or had cardiac surgery. A new home-based cardiac rehab programme was developed known as Rehabilitation Enablement in Chronic Heart Failure (REACH-HF) to support heart failure patients and their caregivers[78]. Although the programme was successful in improving quality of life, there were requests to be able to access the programme online to widen access and participation. In 2020, BHF awarded a grant to Dr Hasnain Dalal and team at the University of Exeter to develop an online digital version of the REACH-HF programme[79]. Offering heart failure patients a digital option in addition to the traditional centre-based modes of delivery could help to address the low uptake of CR in HF. This will help towards meeting the NHS Long Term Plan's goal of increasing the number of people participating in CR.

BHF has also explored other ways of improving access to cardiac rehabilitation, particularly during the COVID-19 pandemic. BHF created a CR online information hub which included an online exercise programme specifically designed for CR patients. By February 2025, the hub had been viewed over 500,000 times.

5) Improving patients' lives

There are an estimated one million people living with heart failure in the UK, causing over 100,000 hospital admissions across the country each year[14]. Patients with heart failure experience various physical and emotional symptoms, which can impact quality of life. Around 80% of patients admitted to hospital with heart failure in the UK are classed as having heart failure that is significantly or extremely life-limiting (New York Heart Association stage III or IV)[15]. But with access to the right services and support, people can go on to have a good quality of life for many years.

BHF-funded research and healthcare programmes have helped to improve the lives of people living with heart failure. BHF-funded researchers contributed to demonstrating how drugs including beta-blockers and ACE inhibitors can help patients live longer and have a better quality of life. Similarly, BHF has helped to increase knowledge around ICD's and pacemakers, specifically how changes to this treatment could improve heart failure symptoms. By demonstrating the value

[14] https://www.bhf.org.uk/-/media/files/for-professionals/research/heart-statistics/bhf-cvd-statistics-uk-factsheet.pdf
[15] https://www.nicor.org.uk/national-cardiac-audit-programme/previous-reports/ncap-and-patient-public-and-carer-reports/ncap-annual-report-2019-final/?layout=default

of home-based health failure specialist nurses, cardiac rehabilitation, and specialist palliative care, BHF programmes have also led to reduced hospital admissions and healthcare cost savings.

6) Conclusion

Since its creation in 1961, BHF has supported research into heart failure. From developing a simple blood test to diagnose heart failure to supporting the development of life saving medicines, BHF research has helped heart failure patients live longer, healthier lives.

Heart failure is often referred to as a pandemic, with around 200,000 new diagnoses every year in the UK[16]. The incidence of heart failure is likely to increase both because of an ageing population and an increase in the number of people surviving heart attacks due to therapeutic advances. In particular, heart failure with preserved fraction (HFpEF) is a growing health concern, making up around half of all heart failure cases, with few drugs that have proved successful. Increasing knowledge of the different mechanisms that cause HF is an urgent challenge and is necessary to choose treatment options.

A big area of interest in heart failure is regenerative medicine. In 2002, scientists amazed the world by showing that a zebrafish heart, unlike a human heart, can completely heal itself after injury, demonstrating the incredible potential of regenerative medicine. The BHF has been supporting this exciting field of research that holds the promise to regrow, repair or replace damaged heart tissue and blood vessels. This can be seen by its investment in three BHF Centres of Regenerative Medicine from 2013 to 2023, and more recently in 2024, joining forces with the MRC to create a new Centre of Research Excellence focussing on heart repair and regeneration. These endeavours may pave the way for a new era of heart failure management.

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[16] https://www.bhf.org.uk/-/media/files/for-professionals/research/heart-statistics/bhf-cvd-statistics-uk-factsheet.pdf

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