British Heart Foundation

A deeper look at the heart

Impact of BHF support for cardiovascular MRI research

April 2022

Impact Thematic review series | Vol 1

Contents

A deeper look at the heart: Impact of BHF support on Cardiovascular Magnetic Resonance research

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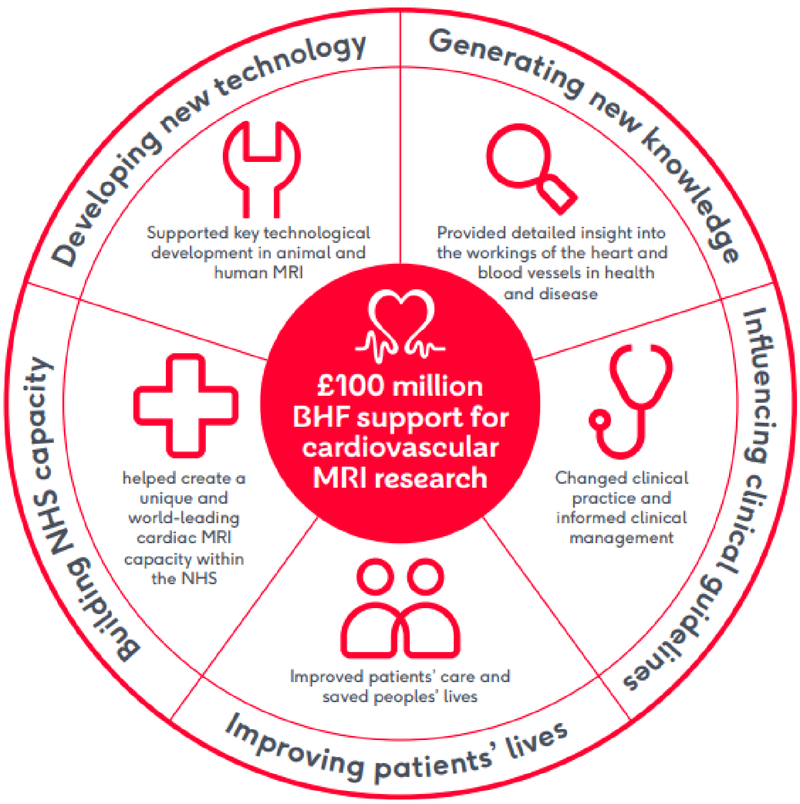
updated February 2022

1. Introduction

Cardiovascular magnetic resonance imaging (MRI) provides highly detailed images of the heart and blood vessels as well as accurate information on the anatomy and function of the cardiovascular system. MRI is non-invasive and safe with no exposure of patients to harmful radiation. Over the past 25 years, cardiovascular MRI has become an important research tool and a mainstream diagnostic test in the National Health Service (NHS).

The British Heart Foundation (BHF) has supported research into cardiovascular MRI from its beginning with more than 250 research grants at a total value of around £100m. This support has included over 100 fellowships at all levels from PhD studentships to personal chairs. The funding has supported key technological developments in animal and human MRI methodology as well as discovery research, which have changed the way we understand the structure and function of the heart in health and disease. The awards have spanned a broad spectrum of heart and circulatory conditions including coronary heart disease, cardiomyopathy, heart failure, congenital heart disease and peripheral vascular disease. BHF-funded research has changed clinical practice and informed clinical management guidelines with direct impact on patients' lives. In addition, BHF support has helped create a unique and world-leading capacity in cardiovascular MRI within the NHS.



2. Developing new technology

MRI is still a relatively young imaging modality which continues to develop and mature. The basic concept of MRI dates back to discoveries by the British Nobel Laureate Peter Mansfield and others in the 1970s, but it wasn't until the late 1980s that MRI for patient scanning was developed. Since then, MRI has become a major clinical tool with over 3.5 million scans of all body parts now undertaken each year in the UK[a]. Imaging the heart and vascular system with MRI poses particular challenges because of the rapid motion of the beating heart. The development of cardiovascular MRI as a research and clinical method has therefore required major technological innovations. BHF funding has supported the very first developments of cardiovascular MRI methodology and is continuing to fund research aimed at developing new methods and improving established applications of cardiovascular MRI.

Summary

- BHF support for the technological foundations of cardiovascular MRI began in the 1980s.
- BHF funding has supported the development of many new cardiovascular MRI methods, including very fast imaging in congenital heart disease.
- A leading example of the impact of BHF funding is the development of heart perfusion imaging from its conception to a routine clinical tool.
- The BHF has made a major contribution to the development of Magnetic Resonance Spectroscopy that allow the study of the energy metabolism of the beating heart.
- The BHF currently supports innovation of methods that allow researchers to see how heart cells are aligned in the normal and diseased heart.

a) Fast imaging

The acquisition of images using MRI is inherently time-consuming, owing to the fundamental physics that underpin the method. Many of the key early technological developments have therefore focussed on speeding up image acquisition. As a result of a series of innovations, many supported by the BHF and led by pioneer Professor Donald Longmore and colleagues at Royal Brompton Hospital in the 1980s and 1990s, image acquisition times in cardiovascular MRI have been reduced from many minutes for a still image 20 years ago to a few seconds or less for moving cine images of the heart today [1-4]. These developments have been instrumental in making cardiovascular MRI a useful diagnostic tool, which can deliver thousands of images of the heart and the vasculature within a single scanning session.

Recently, the BHF has funded research by Professor Vivek Muthurangu and colleagues at University College London that allows image acquisition of the beating heart to be undertaken even faster and in 'real-time' [5-7]. This new technology has already revolutionized cardiovascular MRI in children with congenital heart disease, enabling rapid imaging of the entire heart (<10 minutes total scan time) without sedation in children as young as 6 months old.

The BHF has also supported research by Professor Muthurangu and team where real-time MRI is used during physical exercise in children with pulmonary hypertension which suggested that poor

[a] https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2018/11/Annual-Statistical-Release-2017-18-PDF-1.6MB-1.pdf

exercise capacity is a result of skeletal muscle abnormalities rather than cardiac dysfunction [8]. These findings have opened up a new area of potential treatment for a group of children in whom conventional therapies often fail.

b) Heart perfusion imaging

The coronary arteries deliver oxygen and nutrients to the heart muscle cells and restrictions in blood flow through the coronary arteries can result in symptoms of chest pain (angina) and heart attacks (myocardial infarction). The blood supply to the heart via the coronary arteries can be visualised using contrast-enhanced MRI, a technique called heart perfusion MRI. The potential of this method to influence the management of patients with coronary artery disease was recognised early on. Funding from the BHF has supported the technical development of heart perfusion MRI from its very beginning.

In 1995, the BHF supported Dr James Cullen and colleagues at the University of Leicester to undertake some of the first clinical heart perfusion MRI studies worldwide [9]. Over the following 20 years, the BHF has funded several further research projects that have made these methods faster and more robust. Major grant support to the University of Leeds funded two randomised clinical trials (CE-MARC 1 and CE-MARC 2[a]) led by Professor John Greenwood that showed that heart perfusion MRI is at least as good as other more invasive tests in detecting coronary artery disease and predicting patient outcome, with the advantage of being safer and not using ionising radiation [10]. In 2019, the multi-centre MR-INFORM study led by Professor Eike Nagel at King's College London, which included several BHF-funded researchers and centres, showed that heart perfusion MRI was equivalent to state-of-the-art invasive testing in the catheter laboratory [11]. And in 2020, a BHF-supported study by Professor James Moon and colleagues demonstrated that automatic measurements of heart perfusion MRI in over 1000 patients using a novel artificial intelligence approach can predict which patients are at high risk to suffer a heart attacks or other severe complication [12].

Thanks in large part to these developments, heart perfusion MRI has been given the highest level of recommendation in guidelines published by international cardiology societies for the care of patients with suspected cardiac chest pain and has become a routine diagnostic test in the NHS [13].

c) Metabolic imaging

In addition to imaging the anatomy and function of the heart with MRI, the same scanners can be used to study the metabolism of the heart using the method of magnetic resonance spectroscopy (MRS). Metabolic imaging with MRS provides insight into the way the heart utilises different forms of energy. The BHF has supported the development of MRS for metabolic imaging of the beating heart from its inception all the way to clinical studies. As early as 1982, the 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 [14] and cardiomyopathy [15]. Owing to BHF funding, there is now a network of UK research centres that study the metabolism of the heart using MRS coupled to MRI – including the Universities of Oxford, Leeds, Glasgow, Leicester and Manchester. This capacity is unique worldwide.

Today, the BHF supports the next generation of metabolic MRI that is poised to overcome the relatively low sensitivity of current MRS methods. Pioneering BHF-funded work in Oxford, led by Dr Oliver Rider and colleagues, is establishing a method called hyperpolarized ^{13}C MR

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[a] https://www.bhf.org.uk/what-we-do/our-research/impact-of-clinical-trials/ce-marc-2

spectroscopy which allows metabolic imaging with >10,000-fold increases in sensitivity compared with standard MRS. Such developments have already offered novel insight into heart metabolism in animals and humans that are now being translated to patient studies thanks to further support from the BHF [16, 17].

d) Imaging the microstructure of the heart

Modern cardiovascular MRI methods can delineate the anatomy of the human heart in unparalleled detail. The microstructure of the heart consists of groups of muscle cells (cardiomyocytes) embedded in a fibrous bed (collagen matrix). Cardiomyocytes are arranged in a helix structure that allows both shortening of the heart chambers in multiple directions as well as a twisting motion of the lower and upper parts of the main heart chamber which is essential for the normal beating motion of the heart.

This groups of 5-10 heart muscle cells are organised in so-called sheetlets, a fraction of a millimeter in diameter which contribute importantly to the thickening of the heart muscle in disease. With a method called Diffusion Tensor Imaging (DTI), the diffusion of water along sheetlets can be visualised allowing assessment of the orientation and motion of the sheetlets in the beating heart. DTI has been applied widely in brain imaging, but imaging the heart, which is much more mobile than the brain, has been challenging. Supported by the BHF, researchers at Imperial College London led by Professors Dudley Pennell and David Firmin have developed and validated methods that now allow DTI-MRI in patients and they have already shown that DTI-MRI can image the sheetlets in the human heart [18, 19]. They are now aiming to find out how the arrangement of the sheetlets in the heart changes in a range of diseases, including congenital heart disease and heart attacks. Professor Stefan Neubauer and colleagues in Oxford have used this technique to study sheetlet abnormalities in hypertrophic cardiomyopathy (HCM), a condition characterised by a thickening of the heart muscle and showed that fibre disarray in this condition was associated with potentially dangerous changes in heart rhythm[a] [20].

e) Small animal MRI

Reducing the number of animals needed to answer scientific questions is a major principle of research. The use of modern imaging methods such as MRI allows a reduction in the number of animals required in research studies, because imaging can be performed repeatedly in the same animal. Small animal MRI allows the study of well-defined disease models to better understand disease mechanisms and design new therapies.

MRI is a particularly attractive research tool for small animal imaging because similar methods can be used in animals and in humans, which makes it easier to translate research results to patients. The development of small animal cardiovascular MRI has however been challenging due to the small size and up to 10 times higher heart rates of small animals compared to humans. BHF funding has supported the work of Professor Jurgen Schneider at the University of Oxford and more recently at the University of Leeds to develop, for example, cine-MRI in small animals, a technique that creates short movies of the beating heart using a series of individual picture like in an animation movie, enabling measurement of the heart function [21].

The BHF also helped the wide-spread uptake of small animal MRI in research centres in the UK and beyond. Today, MRI of the heart and blood vessels in small animals is firmly established in much the same way as it is in humans.

[a] https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2019/june/scan-spots-signs-of-future-cardiac-arrest-in-young-people

3. Generating new knowledge

BHF-funded research has led to conceptually new understanding of many disease processes by utilising the unique information MRI can provide about the anatomy of the heart, its global and regional contractile function, iron, fat and fibrosis content and its blood supply and metabolism. Blood vessels can also be studied by MRI, including their detailed anatomy, three-dimensional flow and elasticity. Such detailed assessment provides unique insight into the workings of the heart and circulatory systems in health and disease.

Summary

- BHF-funded work has described how the heart handles the utilisation of different sources of energy, which is now used to develop new treatments for heart failure.
- With support from the BHF, researchers have shown that abnormalities in the orientation of the heart muscle fibres are a key mechanism of heart rhythm abnormalities and sudden death in patients with hypertrophic cardiomyopathy – the most common inherited heart condition.
- BHF-funded work has demonstrated for the first time that fibrosis of the heart plays an important role in late complications of patients born with congenital heart disease.
- BHF-funded research in patients with heart attacks has identified heart muscle bleeding as a key reason for poor outcome.
- Fibrosis in the heart measured with MRI was shown to be related to prognosis in patients with stenosis of the aortic valve.
- Research supported by the BHF has demonstrated the value of measuring blood flow in patients with peripheral vascular disease.
- The BHF has awarded £3m for MRI scanning of 100,000 participants in the ground-breaking UK Biobank study.

a) Cardiac metabolism

Supported by a series of BHF research grants, researchers in Oxford led by Dr Oliver Rider used MR spectroscopy to describe how the beating heart utilises different sources of energy, in particular glucose and fatty acids [22]. The team were able to show how the heart handles energy use at rest and during exercise [23]. 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') [24]. They also showed that this depletion of energy limits exercise capacity in obese people and those with diabetes [25]. 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.

Other research in cardiac metabolism by Professor Stefan Neubauer and colleagues in Oxford has highlighted the central role of a molecule called creatine in the heart. In animal studies, elevated creatine levels protect the heart from injury after a heart attack [26]. The team want to find out now if a change in the transport of creatine can improve the outcome in heart disease.

BHF Professor Sven Plein at the University of Leeds is studying how a recently introduced anti-diabetic drug, called empagliflozin, improves lives of patients with diabetes by studying, among other measurements, the heart's energy use.

With the new method of hyperpolarized spectroscopy, BHF-funded researchers led by Professor Damian Tyler in Oxford have discovered the key role of an enzyme called pyruvate dehydrogenase [27], which is closely involved in energy handling in the heart muscle. This new knowledge is now tested in patient studies aiming to improve the lives of patients with heart failure and diabetes.

b) Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the commonest inherited form of heart disease, affecting approximately 1 in 500 individuals. HCM is also the most common cause of sudden cardiac death in young people, often occurring during physical exertion. Our understanding of the structural and functional changes of the heart muscle in HCM has advanced dramatically because of the ability to study the beating heart in detail with modern MRI methods.

BHF-funded research by Professor Amedeo Chiribiri and colleagues at King's College London and Professor James Moon and colleagues at University College London has led to the discovery that HCM is associated with abnormal blood flow in the small blood vessels of the heart (called microvascular disease) [28, 29].

Research in Oxford by BHF Professor Hugh Watkins and colleagues showed abnormal energy handling of the heart in HCM patients [30]. Further BHF support to Professors Damian Tylerand colleagues has further demonstrated the crucial role of abnormal energy handling during stress [31], as well as abnormal orientation of heart muscle fibres in HCM [20], as mechanisms of heart rhythm abnormalities and sudden death. These findings suggest that MRI can be used to identify HCM patients that are at particular risk of sudden death and who could therefore be selected for treatment, for example with implanted defibrillators. This possibility is currently put to the test in a large international registry of 2,762 HCM patients, the HCM Registry (HCMR), who have all undergone cardiovascular MRI scanning and are now under long-term follow-up. The BHF supports parts of the analysis of HCMR data, led by Professor Stefan Piechnik and colleagues in Oxford, to determine if heart muscle fibrosis can predict the risk of heart rhythm changes.

Because MRI is the most accurate test to measure heart size and function, large clinical studies increasingly rely on this test to measure the effect of new treatments for people with cardiomyopathy and heart failure. Dilated cardiomyopathy (DCM) is a condition where the heart muscle becomes stretched and thin, also called 'baggy', and unable to pump blood around the body efficiently. After coronary heart disease, DCM is the leading cause of heart failure. Recently, the BHF-funded clinical trial TRED-HF led by Professor Sanjay Prasad and colleagues at Royal Brompton Hospital, Imperial College London, showed that patients who have had an episode of heart failure due to dilated cardiomyopathy should continue to take heart failure medication life-long to reduce the risk of a relapse[a] [32]. An ongoing BHF-funded clinical study, GO-DCM led by Professor Stuart Cook, also at Imperial College London, is investigating the interaction between genes and lifestyle factors in 2,000 patients with dilated cardiomyopathy using MRI to find out whether damage to heart muscle, such as scarring, predicts how people with DCM will be affected.

c) Congenital Heart Disease

Although surgery in infancy has revolutionized the treatment of congenital heart disease, declining health due to arrhythmia, premature heart failure and increasing mortality is common as congenital heart disease patients get older. The BHF has funded several research projects that have focused on developing a better understanding of the causes of complications and death in

[a] https://www.bhf.org.uk/what-we-do/our-research/impact-of-clinical-trials/tred-hf-trial

later life for people born with congenital heart diseases. Thanks to BHF funding, research led by Dr Sonya Babu-Narayan and colleagues at Royal Brompton Hospital, Imperial College London, have demonstrated for the first time that fibrosis of the heart plays an important role in late complications in a broad range of congenital heart diseases [33-35]. MRI features were shown to be an important determinant for optimal timing of further surgery after childhood repairs performed to prevent heart failure. MRI scans can also help identify adults with congenital heart disease at highest risk of sudden death.

d) Heart attacks

BHF-funded research has contributed important new knowledge about what happens to the heart after a heart attack, in both animal and patient studies. Professor Colin Berry and colleagues in Glasgow have used BHF grant support to show how 'heart muscle bleeding' (myocardial haemorrhage) can be detected with MRI and how it puts patients at an increased risk of heart failure and death after a heart attack [36]. They also discovered key risk factors for heart muscle bleeding, notably cigarette smoking and high blood pressure [37]. As a result of this and other related research, heart muscle bleeding is now a key target in the search for further improvements of patient outcome at the time of heart attack treatment.

e) Heart valve disease

Heart valve disease is an increasing health problem in an ageing population. When one or more heart valve become damaged or diseased, it can affect the flow of blood through the heart and people with heart valve disease often end up needing treatment with medicines or surgery. BHF funded research using MRI has contributed important new knowledge about the effects of heart valve disease on the heart muscle and other organs. The BHF has supported work at the University of Leicester by Professor Gerry McCann and colleagues that has discovered how blood flow to the heart muscle is linked to symptoms and exercise capacity in patients with aortic valve disease [38]. BHF-funded research in Edinburgh led by Professor Marc Dweck and colleagues showed that fibrosis in the heart is related to prognosis in patients with thickening ('stenosis') of the aortic valve [39]. Another research project led by Professor Stefan Neubauer and colleagues in Oxford improved our understanding of the pathophysiology of ballooning of the aorta, the main body artery, in patients who have abnormal aortic valves that are made of two ('bicuspid') rather than the more common three ('tricuspid') parts [40]. The researchers showed with three-dimensional flow MRI that people with bicuspid aortic valves have abnormal flow patterns in the aorta, exposing the aortic wall to increased mechanical stress.

Several BHF-funded researchers and centres have now formed a Valve Consortium within the British Society of Cardiovascular Magnetic Resonance (BSCMR), which has recently shown that scar in the heart detected by MRI can independently predict the outcome after heart valve replacement [41]. This work was supported by several BHF grants.

f) Peripheral vascular disease

The BHF also funds research into blood vessel health, also called vascular health. Peripheral vascular disease is caused by blockages in the leg arteries, meaning less blood supply can get through, potentially leading to gangrene of the foot and amputation of the lower limb. BHF-funded research led by Professor Bijan Modarai and colleagues at King's College London has recently demonstrated that blood supply to the lower limb can be tracked using an MRI method measuring blood oxygenation. The method showed a reduction in oxygen delivery which improved after stent insertion to remove the blockage [42]. This discovery can now be used in a larger clinical study to determine if blood flow to the leg measured with MRI can guide treatment decisions, improve patients' quality of life, reduce the need for re-interventions and reduce costs to the NHS.

Other BHF funding supported the development of imaging methods to detect blood clot formation in the veins, which is a major cause of illness and can lead to pulmonary embolism and death. In a small animal model, BHF-funded researchers led by Professor Alberto Smith at King's College London have developed an MRI method that may be able to predict if a blood clot in the leg can be dissolved with clot buster medication or if surgery is needed to remove it [43]. This method is now tested in patients.

g) Artificial intelligence and machine learning

Artificial intelligence (AI) and machine learning are rapidly developing areas of research in all imaging methods, including cardiovascular MRI. These methods are changing the way images are acquired and analysed and promise to improve the detection and monitoring of diseases, the screening of potential therapeutic targets and the simulation of interventional procedures. The BHF has funded projects that have shown how AI can predict outcomes in patients with hypertrophic cardiomyopathy, pulmonary hypertension[a] [44], and myocardial infarction [45, 46].

A key requirement for the development of many AI methods is big data, very large sets of data that can be used to train machine learning algorithms. One of the largest current studies is UK Biobank, which is investigating the role of our genes and lifestyle in our risk of developing disease. It includes 500,000 UK participants that are being followed for at least 30 years, with regular collection of a wide variety of health data. The BHF has awarded £3m for cardiac MRI scanning of 100,000 participants. This large-scale database which links MRI scans with genetic, outcome, and many other data, will provide a unique opportunity to establish imaging biomarkers of cardiovascular risk, and a platform for developing AI and machine learning based techniques.

Additional BHF support to Professor Steffen Petersen and colleagues at Queen Mary University London has allowed the manual analysis of the first 5,000 MRI scans from the UK Biobank which has trained machine learning algorithms that can now analyse all data sets. Using MRI data from UK Biobank, the team have already developed a new heart-specific image analysis 'toolkit', called 'CMR radiomics' and showed that the heart of men and women have different shapes and texture – findings that will now be expanded to other groups at risk of heart disease[b] [47]. Future research will link these analyses to UK Biobank subjects' genetic profile, blood markers, lifestyle, blood pressure, clinical outcomes and many other measurements taken as part of the UK Biobank assessment. It is expected that this research will lead to major new discoveries about individual risk profiles for the development of heart and circulatory diseases.

BHF-funded researchers from Imperial College London led by Professor Declan O'Regan used AI to analyse cardiac MRI scans of over 18,000 people from the 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[c] [48].

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[a] https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2019/february/artificial-intelligence-predicts-outcomes-for-heart-patients

[b] https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2020/august/esc-heart-shape-structure-men-women-qmul

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

h) Covid-19

In response to the Covid-19 pandemic, the BHF supported a number of efforts using MRI to determine the effects of Covid-19 infection on the heart. Meanwhile, BHF-funded researchers in Edinburgh led by Professor Marc Dweck showed as part of a world-wide survey of 69 countries that Covid-19 infection can affect heart function[a] [49].

One of seven NIHR-BHF flagship projects, co-led by Professor John Greenwood in Leeds and Professor Stefan Neubauer in Oxford, aimed to characterise the prevalence and extent of heart muscle and multi-organ damage using MRI in patients who have suffered a mild severe acute respiratory syndrome-coronavirus-2 infection, and assessed their recovery status after six months[b]. The findings, published in 2021, showed that six months after infection, cardiovascular abnormalities are no more common in people who had been infected with the virus when compared with people who hadn't [50].

4. Influencing clinical guidelines

MRI has become a routine clinical test for the detection of heart and circulatory diseases and to guide the management of people living with those conditions. The UK is leading world-wide not only in MRI research but also in adopting cardiovascular MRI into routine clinical practice, enabling better diagnosis, better treatment and better outcomes for many patients with heart and circulatory diseases. BHF-funded research has been instrumental for this remarkable transition of MRI from research tool to mainstream clinical practice. The impact of BHF-funded MRI research is reflected in the clinical practice guidelines published by international cardiology societies, which summarise the available evidence for diagnostic tests and treatments to guide physicians in their daily care of patients. More than half of the current European Society of Cardiology (ESC) clinical practice guidelines include specific recommendations on the use of MRI or mention MRI in the guideline text. In many instances BHF-funded research has directly informed these guidelines.

[a] https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2020/july/heart-scans-abnormal-in-covid-19

[b] https://www.bhf.org.uk/for-professionals/information-for-researchers/national-flagship-projects

Summary

- BHF funded research in MRI has changed the way many people with heart disease are managed.
- National and international clinical practice guidelines now define the role of MRI in diagnosis and treatment of people with many forms of heart disease, often informed by BHF-funded research.
- In coronary artery disease, current European and US guidelines include the highest level of recommendation for the use of cardiac MRI, based in part on BHF-funded clinical trials.
- In heart failure, cardiovascular MRI is now the standard tool to measure the size and function of the main heart chambers due to its superior accuracy compared with other tests. Using MRI in clinical trials allows substantial reductions in the number of patients that need to be studied.
- BHF-supported research has contributed important findings to the latest European guidelines for the routine use of MRI in hypertrophic cardiomyopathy, amyloidosis and Fabry's disease.
- In congenital heart disease, MRI is today a routine test for all children and adults with clear international guideline indications for frequency of repeat imaging tests, owing in many cases to BHF-funded research.

a) Coronary artery disease

Several BHF-funded studies have demonstrated the utility of cardiovascular MRI in the detection and treatment guidance of patients with coronary artery disease and have informed international practice guidelines. In patients with new onset of chest pain, the ESC [13], and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of stable coronary artery disease include a recommendation for using MRI to determine if heart disease is the cause of chest pain in patients with intermediate risk of having heart disease. The evidence for this recommendation includes the BHF-funded CE-MARC and CE-MARC 2 studies[a] led by Professor John Greenwood and colleagues in Leeds which have demonstrated the accuracy of MRI in detecting coronary artery disease and its ability to avoid unnecessary invasive heart tests in these patients [10].

b) Congenital heart disease

The availability of cardiovascular MRI has dramatically changed the way people with congenital heart disease are managed. Today MRI is an irreplaceable test for the diagnosis and long-term management of congenital heart disease patients, owing to its three-dimensional coverage of the heart and blood vessels, high image quality and its ability to delineate the anatomy of the heart as well as key functional parameters such as flow in the main blood vessels. Because MRI does not use harmful radiation, it is also the favoured test in young patients who often need multiple scans in their lives and where repeated x-ray exposure needs to be avoided. The change in clinical practice to the routine use of MRI in congenital heart disease has been enabled in part by BHF-funded research by Professor Edward Baker and colleagues at Guy's Hospital, King's College London, which initially demonstrated the utility of cardiovascular MRI in children with heart disease. Several research publications [34, 51, 52] that have arisen from BHF-funded studies

[a] https://www.bhf.org.uk/what-we-do/our-research/impact-of-clinical-trials/ce-marc-2

or have been conducted by BHF-funded researchers have been cited as key evidence in the 2010 ESC clinical practice guidelines for the management of grown-up congenital heart disease [53].

c) Cardiomyopathy

Cardiovascular MRI today plays a key role in identifying patients with cardiomyopathy and in the screening of family members with inherited forms of heart disease. MRI offers consistently high image quality for the assessment of the size of the heart chambers and heart muscle and also allows detection of fibrosis (scarring) in the heart muscle which can occur in different forms of cardiomyopathy. In hypertrophic cardiomyopathy, European guidelines now recommend that all patients with the condition should undergo an MRI scan at least once following diagnosis [54]. In making this recommendation, the guidelines refer to several studies which were conducted by BHF-funded researchers or in BHF-funded research centres and showed for example the importance of scarring in the heart in hypertrophic cardiomyopathy and related conditions [55-57].

5. Improving patients' lives

Major improvements in patient care require the support of multiple funding bodies and are achieved through international research efforts. BHF-funded research into CMR contributed to improve the lives of patients with a wide range of heart and circulatory conditions.

Summary

- BHF funded research has supported the development and nationwide introduction of iron measurement in the heart, which has eliminated the risk of death from heart failure in patients with thalassaemia major.
- In heart attack patients, studies supported by the BHF contribute to the ongoing improvements in the survival of patients using detailed MRI scanning to guide treatment.
- Research supported by BHF projects, fellowships and infrastructure grants has led to replacing higher risk invasive diagnostic cardiac catheterization in patients with congenital heart disease.

a) Iron overload cardiomyopathy

Thalassemia major is an inherited disorder of haemoglobin affecting an estimated 100,000 patients world-wide, which leads to chronic anaemia. Most patients with thalassemia major typically require blood transfusions from birth in order to survive. Over time, iron from transfused blood accumulates in the body, including in the heart where chronic iron overload leads to heart failure, which is the most common cause of death in thalassemia patients. Treatments that remove excess iron from the body ('chelation therapy') are available today and can effectively prevent heart failure, but until the 1990s there was no safe method to measure the iron loading in the heart and determine the success of treatment. The "T2-star" (T2*) MRI technique, established at the Royal Brompton Hospital & Imperial College London by Professor Dudley Pennell and his team was initially developed thanks to BHF funding in the late 1990s, and revolutionised the management of iron overload. T2* values by MRI are directly correlated with the iron content of the heart muscle and can be used to detect iron overload and monitor the effect of iron chelation treatment [58-60]. Since the introduction of chelation therapy and T2* MRI monitoring, mortality rates in thalassemia major in the UK have dramatically reduced and are now similar to those of the general population. A major programme of introducing T2* MRI around the world, based on the research conducted in the UK, has seen similar improvements in mortality. BHF-funded research over two decades has made a major contribution to preventing death from iron overload cardiomyopathy and has saved many lives[a].

b) Heart attacks

Heart attacks remain one of the leading causes of disability and death in the UK. The effects of heart attacks on the heart can be measured most accurately with MRI, including the extent of heart muscle damage and its complications such as bleeding into the heart muscle and obstruction of the small blood vessels in the heart. MRI is therefore increasingly used in clinical trials that compare heart attack treatments and test the effects of new treatments. Such trials are essential to further improve patient outcome after a heart attack.

The BHF has supported several studies in which MRI was used as the study endpoint. One of these studies, the ERIC-PPCI clinical trial led by Professors Derek Haunsenloy and Derek Yellon at University College London, investigated a procedure called 'post-conditioning' in which a blood pressure cuff on the arm is inflated several times and showed that while it reduces the size of a heart muscle damage in patients with an acute heart attack it does not improve long term survival of heart attack victims[b] [61].

BHF support to Professor Colin Berry and colleagues in Glasgow enabled the MRI sub-study in the landmark PRAMI clinical trial who was looking at the effectiveness of preventive angioplasty in heart attacks [62]. The BHF-funded MRI sub-study of PRAMI showed that stenting multiple heart arteries in heart attack patients is not harmful [63].

Clinical studies supported by the BHF contribute to the ongoing improvements in the care of heart attack patients with more patients surviving heart attacks and fewer patients suffering the long-term adverse consequences of a heart attack such as heart failure.

c) Congenital heart disease

Several BHF funded studies have had a significant impact on the management of patients with congenital heart disease. Early studies into the utility of MRI in children with heart disease, led by BHF-funded Professor Ted Baker and colleagues at King's College London in the 1980s, have resulted in this test now being routinely used in these patients across the UK to replace higher risk invasive diagnostic cardiac catheterization. In addition, BHF support to Professors Baker and Reza Razavi's team helped to develop MR guided and augmented cardiac catheterization[c] . This technique is used for example to measure the resistance in the lungs in children and adults with congenital heart disease. The benefit of this technique is more accurate measurements and no exposure to harmful ionizing radiation. As a result of the work carried out by BHF-funded researchers this technique is now being disseminated to the wider community and is on the cusp of becoming clinical routine.

[a] https://impact.ref.ac.uk/casestudies/CaseStudy.aspx?Id=42188

[b] https://www.bhf.org.uk/what-we-do/our-research/impact-of-clinical-trials/eric-ppci-trial

[c] https://impact.ref.ac.uk/casestudies/CaseStudy.aspx?Id=41233

6. Building NHS capacity

The UK today has one of the largest numbers of experts in cardiovascular MRI and one of the highest densities of hospitals that offer cardiovascular MRI in the world. The development of this infrastructure has been enabled in large part by more than three decades of BHF support. In the early 1990s the BHF provided funding for cardiovascular MRI at the Royal Brompton Hospital in London and to establish a group in Oxford. Both centres become some of the first international hubs for MRI research. Other BHF-funded centres, including Leeds, Edinburgh and Glasgow, followed soon after. Today, more than 100 BHF-funded clinical research fellows have undertaken cardiovascular MRI research and during their fellowships have been trained to become experts in clinical cardiovascular MRI. Many of these are now leading MRI services as NHS consultants and or clinical academics. Several university hospitals run BHF-supported research programmes that are seamlessly integrated with local clinical cardiovascular MRI services. This spread of highly trained specialists over several generations has made a major contribution to the sustained growth of cardiovascular MRI in the UK. According to the latest survey of the British Society of Cardiovascular Magnetic Resonance, 82 NHS hospitals offered cardiovascular MRI services in 2018, with over 100,000 cardiovascular MRI scans in adults now performed in the UK per year[a]. In addition, all of the UK's tertiary congenital heart disease centres have MRI facilities giving access to cardiovascular MRI scans to children with heart disease and sparing many of them more harmful or invasive investigations.

Summary

- Enabled by more than three decades of BHF support, the UK today has one of the largest numbers of experts in cardiovascular MRI and one of the highest densities of hospitals that offer cardiovascular MRI in the world.
- Over 100 BHF-funded fellows have been trained in clinical cardiovascular MRI.
- All the UK's congenital heart disease centres have cardiovascular MRI facilities, reducing exposure to harmful radiation and invasive tests.

a) Cardiovascular MRI centres in the UK

The UK has among the highest densities of clinical cardiovascular MRI facilities worldwide. Some of these are affiliated with leading research sites which received infrastructure funding from the BHF via Infrastructure awards (for example in Oxford, Glasgow, Leeds, Manchester and Leicester) or were set up by BHF-funded individuals and supported by major BHF research grants. The synergistic development of cardiovascular MRI research and clinical practice in the UK has ensured the highest standard of care for NHS patients through access to the latest technology and evidence and gives all NHS patients access to a safe and highly versatile imaging modality.

Alongside the development of MRI, BHF funding has allowed the training of a new specialty of cardiovascular MRI radiographers. Often involved in both research and clinical scanning, these highly trained individuals provide a uniquely qualified workforce for the NHS.

[a] https://programme.escardio.org/ESC2020/Abstracts/215501-uk-national-and-regional-trends-in-cardiovascular-magnetic-resonance-usage-the-british-society-of-cmr-survey-results

b) Congenital MRI centres

All the UK's congenital heart disease centres have access to cardiovascular MRI facilities. It is estimated that more than 10,000 congenital heart disease MRI scans are undertaken in the UK each year[a], meaning less exposure to harmful radiation and reduced risk from invasive tests in this patient group [64]. BHF funding has been pivotal in the training of generations of specialists in MRI of congenital heart disease and pulmonary hypertension, a common complication of congenital heart disease. These imaging specialists, including two previous BHF Intermediate Clinical ResearchRfellows, Dr Sonya Babu-Narayan and Professor Vivek Muthurangu, now run most of the large clinical MRI centres that deal with congenital heart disease and use their expertise to improve patient management.

c) Preclinical MRI centres

In parallel with the support for clinical MRI centres, the BHF has funded preclinical Magnetic Resonance scanners and infrastructure at four universities (KCL, UCL, Edinburgh and Oxford) in the second cardiovascular initiative, and more recently in Leeds. These centres have put the UK at the forefront of preclinical MRI research.

7. Conclusion

The development of cardiovascular MRI has changed the way we conduct research into heart and circulatory disease and how we practice clinical medicine today. The BHF has been instrumental in setting up a network of research and clinical centres across the whole of the UK, which has delivered key methodological improvements that have made MRI practical for routine cardiovascular imaging, has provided unique insight into many forms of heart disease and has had direct impact on how patients with heart disease can be identified and treated. MRI remains a highly active, rapidly developing field, and many more projects, programmes and fellowships are underway that will build on what BHF-funded MRI research has already delivered, with more ground-breaking science and technical advances expected in coming years.

8. References

1. Forbat, S.M., et al., *Technical note: rapid measurement of left ventricular mass by spin echo magnetic resonance imaging.* Br J Radiol, 1994. **67**(793): p. 86-90.
2. Karwatowski, S.P., et al., *Regional myocardial velocity imaged by magnetic resonance in patients with ischaemic heart disease.* Br Heart J, 1994. **72**(4): p. 332-8.
3. Kilner, P.J., et al., *Magnetic resonance jet velocity mapping in mitral and aortic valve stenosis.* Circulation, 1993. **87**(4): p. 1239-48.
4. Pennell, D.J., S.R. Underwood, and D.B. Longmore, *Improved cine MR imaging of left ventricular wall motion with gadopentetate dimeglumine.* J Magn Reson Imaging, 1993. **3**(1): p. 13-9.
5. Kowalik, G.T., et al., *Rapid breath-hold assessment of myocardial velocities using spiral UNFOLD-ed SENSE tissue phase mapping.* J Magn Reson Imaging, 2016. **44**(4): p. 1003-9.
6. Steeden, J.A., et al., *Real-time assessment of right and left ventricular volumes and function in children using high spatiotemporal resolution spiral bSSFP with compressed sensing.* J Cardiovasc Magn Reson, 2018. **20**(1): p. 79.

[a] https://programme.escardio.org/ESC2020/Abstracts/215501-uk-national-and-regional-trends-in-cardiovascular-magnetic-resonance-usage-the-british-society-of-cmr-survey-results

7. Steeden, J.A., et al., *Rapid whole-heart CMR with single volume super-resolution.* J Cardiovasc Magn Reson, 2020. **22**(1): p. 56.
8. Barber, N.J., et al., *Magnetic Resonance-Augmented Cardiopulmonary Exercise Testing: Comprehensively Assessing Exercise Intolerance in Children With Cardiovascular Disease.* Circ Cardiovasc Imaging, 2016. **9**(12).
9. Cullen, J.H., et al., *A myocardial perfusion reserve index in humans using first-pass contrast-enhanced magnetic resonance imaging.* J Am Coll Cardiol, 1999. **33**(5): p. 1386-94.
10. Greenwood, J.P., et al., *Effect of Care Guided by Cardiovascular Magnetic Resonance, Myocardial Perfusion Scintigraphy, or NICE Guidelines on Subsequent Unnecessary Angiography Rates: The CE-MARC 2 Randomized Clinical Trial.* JAMA, 2016. **316**(10): p. 1051-60.
11. Nagel, E., et al., *Magnetic Resonance Perfusion or Fractional Flow Reserve in Coronary Disease.* N Engl J Med, 2019. **380**(25): p. 2418-2428.
12. Knott, K.D., et al., *The Prognostic Significance of Quantitative Myocardial Perfusion: An Artificial Intelligence-Based Approach Using Perfusion Mapping.* Circulation, 2020. **141**(16): p. 1282-1291.
13. Montalescot, G., et al., *2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology.* Eur Heart J, 2013. **34**(38): p. 2949-3003.
14. Kemp, G.J., et al., *Abnormalities in exercising skeletal muscle in congestive heart failure can be explained in terms of decreased mitochondrial ATP synthesis, reduced metabolic efficiency, and increased glycogenolysis.* Heart, 1996. **76**(1): p. 35-41.
15. Thompson, C.H., et al., *Abnormal skeletal muscle bioenergetics in familial hypertrophic cardiomyopathy.* Heart, 1997. **78**(2): p. 177-81.
16. Burrage, M.K., et al., *Energetic Basis for Exercise-Induced Pulmonary Congestion in Heart Failure With Preserved Ejection Fraction.* Circulation, 2021. **144**(21): p. 1664-1678.
17. Ding, B., et al., *Water-suppression cycling 3-T cardiac.* NMR Biomed, 2021. **34**(7): p. e4513.
18. Ferreira, P.F., et al., *In vivo cardiovascular magnetic resonance diffusion tensor imaging shows evidence of abnormal myocardial laminar orientations and mobility in hypertrophic cardiomyopathy.* J Cardiovasc Magn Reson, 2014. **16**: p. 87.
19. Nielles-Vallespin, S., et al., *Assessment of Myocardial Microstructural Dynamics by In Vivo Diffusion Tensor Cardiac Magnetic Resonance.* J Am Coll Cardiol, 2017. **69**(6): p. 661-676.
20. Ariga, R., et al., *Identification of Myocardial Disarray in Patients With Hypertrophic Cardiomyopathy and Ventricular Arrhythmias.* J Am Coll Cardiol, 2019. **73**(20): p. 2493-2502.
21. Koth, J., et al., *High-Resolution Magnetic Resonance Imaging of the Regenerating Adult Zebrafish Heart.* Sci Rep, 2017. **7**(1): p. 2917.
22. Scheuermann-Freestone, M., et al., *Abnormal cardiac and skeletal muscle energy metabolism in patients with type 2 diabetes.* Circulation, 2003. **107**(24): p. 3040-6.
23. Neubauer, S., *The failing heart--an engine out of fuel.* N Engl J Med, 2007. **356**(11): p. 1140-51.
24. Mahmod, M., et al., *The interplay between metabolic alterations, diastolic strain rate and exercise capacity in mild heart failure with preserved ejection fraction: a cardiovascular magnetic resonance study.* J Cardiovasc Magn Reson, 2018. **20**(1): p. 88.
25. Rider, O.J., et al., *Noninvasive In Vivo Assessment of Cardiac Metabolism in the Healthy and Diabetic Human Heart Using Hyperpolarized.* Circ Res, 2020. **126**(6): p. 725-736.
26. Lygate, C.A., et al., *Moderate elevation of intracellular creatine by targeting the creatine transporter protects mice from acute myocardial infarction.* Cardiovasc Res, 2012. **96**(3): p. 466-75.

27. Atherton, H.J., et al., *Role of pyruvate dehydrogenase inhibition in the development of hypertrophy in the hyperthyroid rat heart: a combined magnetic resonance imaging and hyperpolarized magnetic resonance spectroscopy study.* Circulation, 2011. **123**(22): p. 2552-61.
28. Camaioni, C., et al., *Inline perfusion mapping provides insights into the disease mechanism in hypertrophic cardiomyopathy.* Heart, 2020. **106**(11): p. 824-829.
29. Villa, A.D., et al., *Microvascular ischemia in hypertrophic cardiomyopathy: new insights from high-resolution combined quantification of perfusion and late gadolinium enhancement.* J Cardiovasc Magn Reson, 2016. **18**: p. 4.
30. Crilley, J.G., et al., *Hypertrophic cardiomyopathy due to sarcomeric gene mutations is characterized by impaired energy metabolism irrespective of the degree of hypertrophy.* J Am Coll Cardiol, 2003. **41**(10): p. 1776-82.
31. Dass, S., et al., *Exacerbation of cardiac energetic impairment during exercise in hypertrophic cardiomyopathy: a potential mechanism for diastolic dysfunction.* Eur Heart J, 2015. **36**(24): p. 1547-54.
32. Halliday, B.P., et al., *Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial.* Lancet, 2019. **393**(10166): p. 61-73.
33. Babu-Narayan, S.V., et al., *Late gadolinium enhancement cardiovascular magnetic resonance of the systemic right ventricle in adults with previous atrial redirection surgery for transposition of the great arteries.* Circulation, 2005. **111**(16): p. 2091-8.
34. Babu-Narayan, S.V., et al., *Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome.* Circulation, 2006. **113**(3): p. 405-13.
35. Rydman, R., et al., *Systemic right ventricular fibrosis detected by cardiovascular magnetic resonance is associated with clinical outcome, mainly new-onset atrial arrhythmia, in patients after atrial redirection surgery for transposition of the great arteries.* Circ Cardiovasc Imaging, 2015. **8**(5).
36. Carrick, D., et al., *Comparative Prognostic Utility of Indexes of Microvascular Function Alone or in Combination in Patients With an Acute ST-Segment-Elevation Myocardial Infarction.* Circulation, 2016. **134**(23): p. 1833-1847.
37. Haig, C., et al., *Current Smoking and Prognosis After Acute ST-Segment Elevation Myocardial Infarction: New Pathophysiological Insights.* JACC Cardiovasc Imaging, 2019. **12**(6): p. 993-1003.
38. Steadman, C.D., et al., *Determinants and functional significance of myocardial perfusion reserve in severe aortic stenosis.* JACC Cardiovasc Imaging, 2012. **5**(2): p. 182-9.
39. Dweck, M.R., et al., *Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis.* J Am Coll Cardiol, 2011. **58**(12): p. 1271-9.
40. Lorenz, R., et al., *4D flow magnetic resonance imaging in bicuspid aortic valve disease demonstrates altered distribution of aortic blood flow helicity.* Magn Reson Med, 2014. **71**(4): p. 1542-53.
41. Musa, T.A., et al., *Myocardial Scar and Mortality in Severe Aortic Stenosis.* Circulation, 2018. **138**(18): p. 1935-1947.
42. Bajwa, A., et al., *Blood Oxygenation Level-Dependent CMR-Derived Measures in Critical Limb Ischemia and Changes With Revascularization.* J Am Coll Cardiol, 2016. **67**(4): p. 420-431.
43. Saha, P., et al., *Magnetic resonance T1 relaxation time of venous thrombus is determined by iron processing and predicts susceptibility to lysis.* Circulation, 2013. **128**(7): p. 729-736.
44. Attard, M.I., et al., *Metabolic pathways associated with right ventricular adaptation to pulmonary hypertension: 3D analysis of cardiac magnetic resonance imaging.* Eur Heart J Cardiovasc Imaging, 2019. **20**(6): p. 668-676.

45. Gao, H., et al., *Estimating prognosis in patients with acute myocardial infarction using personalized computational heart models.* Sci Rep, 2017. **7**(1): p. 13527.
46. Mangion, K., et al., *Advances in computational modelling for personalised medicine after myocardial infarction.* Heart, 2018. **104**(7): p. 550-557.
47. Petersen, S.E., et al., *Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort.* J Cardiovasc Magn Reson, 2017. **19**(1): p. 18.
48. Meyer, H.V., et al., *Genetic and functional insights into the fractal structure of the heart.* Nature, 2020. **584**(7822): p. 589-594.
49. Dweck, M.R., et al., *Global evaluation of echocardiography in patients with COVID-19.* Eur Heart J Cardiovasc Imaging, 2020. **21**(9): p. 949-958.
50. Joy, G., et al., *Prospective Case-Control Study of Cardiovascular Abnormalities 6 Months Following Mild COVID-19 in Healthcare Workers.* JACC Cardiovasc Imaging, 2021. **14**(11): p. 2155-2166.
51. Diller, G.P., et al., *Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication.* Circulation, 2005. **112**(6): p. 828-35.
52. Frigiola, A., et al., *Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome?* Circulation, 2008. **118**(14 Suppl): p. S182-90.
53. Baumgartner, H., et al., *ESC Guidelines for the management of grown-up congenital heart disease (new version 2010).* Eur Heart J, 2010. **31**(23): p. 2915-57.
54. Cardim, N., et al., *Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy: an expert consensus of the European Association of Cardiovascular Imaging Endorsed by the Saudi Heart Association.* Eur Heart J Cardiovasc Imaging, 2015. **16**(3): p. 280.
55. Moon, J.C., et al., *Gadolinium enhanced cardiovascular magnetic resonance in Anderson-Fabry disease. Evidence for a disease specific abnormality of the myocardial interstitium.* Eur Heart J, 2003. **24**(23): p. 2151-5.
56. O'Hanlon, R., et al., *Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy.* J Am Coll Cardiol, 2010. **56**(11): p. 867-74.
57. Sado, D.M., et al., *Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping.* Circ Cardiovasc Imaging, 2013. **6**(3): p. 392-8.
58. Carpenter, J.P., et al., *International survey of T2* cardiovascular magnetic resonance in β-thalassemia major.* Haematologica, 2013. **98**(9): p. 1368-74.
59. He, T., et al., *Myocardial T2* measurements in iron-overloaded thalassemia: An in vivo study to investigate optimal methods of quantification.* Magn Reson Med, 2008. **60**(5): p. 1082-9.
60. Kirk, P., et al., *Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major.* Circulation, 2009. **120**(20): p. 1961-8.
61. Hausenloy, D.J., et al., *Effect of remote ischaemic conditioning on clinical outcomes in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial.* Lancet, 2019. **394**(10207): p. 1415-1424.
62. Wald, D.S., et al., *Randomized trial of preventive angioplasty in myocardial infarction.* N Engl J Med, 2013. **369**(12): p. 1115-23.
63. Mangion, K., et al., *Infarct size and left ventricular remodelling after preventive percutaneous coronary intervention.* Heart, 2016. **102**(24): p. 1980-1987.
64. Razavi, R., et al., *Cardiac catheterisation guided by MRI in children and adults with congenital heart disease.* Lancet, 2003. **362**(9399): p. 1877-82.