British Heart Foundation

At the cutting edge of surgery

Impact of BHF support for cardiovascular surgery research

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At the cutting edge of surgery: Impact of BHF support for cardiovascular surgery research

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1) Introduction

Cardiovascular surgery has developed hugely over the last 60 years in terms of both the breadth of its importance in treating a wide range of cardiovascular diseases, as well as major improvements in associated morbidity and mortality.

Until the early 1950s, there had been very little that a surgeon could hope to achieve by operating on an organ as complex and as constantly in motion as the heart. This all changed with the development of cardiopulmonary bypass (CPB). During CPB a pump, usually referred to as a heart-lung machine, takes over the function of the heart and lungs to maintain the circulation of blood and oxygen around the body during surgery.

The 1960s and 1970s were largely occupied by the development of basic techniques particularly associated with the surgical treatment of coronary heart disease, valvular heart disease, diseases of the thoracic aorta and paediatric and adult cardiac surgery for congenital heart disease. It was during the 1980s and 1990s where significant research efforts were put into investigating almost every area of cardiovascular surgery to reduce the obvious morbidity and mortality associated with cardiac surgical procedures. This was particularly of relevance as the population undergoing cardiac surgery evolved to include a significantly older cohort with associated comorbidities, making the risk of complications more significant.

Recent years, since the millennium, have seen further efforts to develop predominantly less invasive interventions and surgical approaches which add further refinement to cardiac surgical procedures and may result in less physiological disruption.

Since its creation in 1961, the BHF has supported wide ranging research initiatives across the cardiovascular spectrum which have been invaluable in transforming modern cardiac surgery into the routine and safe procedures that are undertaken today. The BHF has awarded over 500 grants worth over £80M funding all stages of research, from discovery science to clinical studies.

The field of research in cardiovascular surgery is broad. In this review we have focused on specific areas of importance where BHF-funded research has been sustained and impactful. The topics covered here are:

- **Cardiopulmonary bypass (CPB):** a technique where a machine temporarily takes over the function of the heart and lungs during heart surgery.
- **Coronary artery bypass graft (CABG) surgery**: an operation used to treat coronary artery disease.
- **Heart valve replacement:** to repair or replace damaged or diseased heart valves that ensure the blood flows through the heart in the correct direction.
- **Heart transplantation**: for people with end stage heart failure, often due to damage sustained from a heart attack but also occurring in cardiomyopathies and congenital heart diseases.
- **Perioperative care:** including all phases of pre-operative (e.g., assessing the risk of surgery), intra-operative (e.g., myocardial protection, managing fluids, anesthesia, blood conservation) and post-operative (e.g., recovery, short or long term follow up) care.

- **Pediatric cardiovascular surgery:** heart surgery in children to treat complex congenital heart defects.

2) Cardiopulmonary bypass (CPB)

a) Cardiopulmonary bypass perfusion

During surgery, the heart-lung machine takes over the function of the heart and lungs to maintain the circulation of blood and oxygen around the body (also called perfusion). In the 1970s, the BHF funded Dr Ken Taylor's research in Glasgow to compare the benefits of continuous perfusion with pulsatile perfusion (considered to be more physiological) to perform heart surgery while on CPB. Significant benefits were identified in a series of reports widely accepted as groundbreaking, including lower mortality in the 'pulsatile group'[1-4]. To this day, the benefits of pulsatile perfusion remains a longstanding debate and are still being actively investigated.

b) Complications of cardiopulmonary bypass

CPB can be associated with complications in various organs, including the lungs, brain, kidneys and eyes. Since the 1980s the BHF has been funding research to understand how these complications are triggered to find ways to prevent them.

i. The role of inflammation

The BHF funded the work of Dr Dave Royston and colleagues at Hammersmith Hospital in London in the 1980s to understand the causes of lung injuries during CPB. Royston and colleagues identified the key role of inflammation in this process. During CPB, the contact of blood with the foreign surface of the tubes and oxygenator of the heart-lung machine can activate immune cells, altering their motility. The team showed that these immune cells can then travel to the lungs where they are trapped. They start releasing pro-oxidant molecules which can damage the lungs, causing injury.

In 1983, Professor Taylor took up the BHF Chair of Cardiac Surgery at Hammersmith Hospital in London and continued to undertake groundbreaking research into the pathophysiology of CPB, in particular trying to understand and limit its damaging effects by studying the role of the systemic inflammatory response. Professor Taylor and colleagues deciphered the molecular mechanisms involved in the inflammation of cardiac tissue in response to CPB and identified the link between fibrinolytic activity (the process preventing the formation of blood clots) in the heart tissue and local inflammation [5-7].

These discoveries opened new therapeutic avenues to prevent complications caused by CPB. Working closely with Dr Dorian Haskard (who later became BHF Professor of Cardiovascular Medicine), Professor Taylor published a series of papers first demonstrating the value of treatment with aprotinin, an antifibrinolytic also known as Trasylol™, to reduce inflammation induced by CPB [8]. The team also made the serendipitous discovery that aprotinin dramatically reduced blood loss around the time of surgery [9], one of the most important research discoveries in the cardiac surgical field in the latter part of the twentieth century. Though aprotinin is still used in cardiac surgery to control bleeding, tranexamic acid, an alternative anti-fibrinolytic agent that also reduces inflammation, is now more commonly used to minimize bleeding and limit inflammation induced by CPB.

In 2018, the BHF awarded a translational grant to Dr Gregory Quinlan and his team at Imperial College London to develop a new technology to prevent inflammation during CPB. The red blood cells re-routed through the heart-lung machine are at risk of rupturing, a process called haemolysis. This can cause the release of potentially harmful molecules, including haemoglobin, haem and iron, which can contribute to inflammation and increase the risk of organ injury and complications. Dr Quinlan and colleagues have developed a filter that can be fitted within the heart-lung machine to

remove these harmful molecules. This translational grant will help the team further improve their model. If successful, it would become the first effective filter device that can prevent complications caused by haemolysis and help improve outcomes of surgery[a].

ii. Cerebral complications

In the 1980s, there was also a significant focus on the neurological and neuropsychological impacts of CPB. The BHF funded Dr (now Professor Dame) Pamela Shaw's junior fellowship at the University of Newcastle, where she identified the significant neurological and neuropsychological complications of CABG surgery [10, 11]. The BHF also funded the work of Professor Tom Treasure at St George's University London and Dr Peter Smith at Imperial College London who, in association with Professor Stanton Newman at University College London, also provided additional insights into the cerebral consequences of CPB [12, 13]. In the meantime, Professor Taylor undertook a series of studies using retinal photography to demonstrate the microembolism (fragments of blood clots trapped in small blood vessels) occurring in association with CPB, presumed to be the mechanism of such detrimental effects [14].

Despite major advances in the field of cardiovascular surgery, neurological complications persist, including ischaemic stroke and cognitive decline. The risk of stroke can vary from 1% for CABG surgery to 3-9% for surgeries involving cardiac valves and the aorta[b]. The risk of stroke is even higher in patients who develop atrial fibrillation after heart surgery. This is why the BHF has been funding research to understand how atrial fibrillation develops after cardiovascular surgery, to better prevent and treat it (further developed in section 6c).

iii. End-organ complications

More recently BHF Professor Gavin Murphy and colleagues at the University of Leicester have investigated a range of approaches to ameliorate the damaging effects of CPB on end-organ function, this refers to damage to major organs perfused by the circulatory system. The team developed a pig model to elucidate the mechanisms of end-organ complications induced by CPB and identified the key role of nitric oxide, which dilates blood vessels, in protection from kidney injury associated with CBP [15]. The use of sildenafil, a drug that enhances the dilation of blood vessels induced by nitric oxide, showed benefits in the pig model [16]. However, when tested in humans (ReVAKI-1 Trial), no protective effect of the therapeutic intervention was identified [17].

3) Coronary artery bypass graft surgery (CABG)

Coronary heart disease (CHD) develops when the coronary arteries become narrowed by a build-up of fatty material within their walls – also called atheroma. CHD develops slowly over time and can present with various symptoms, including chest pain and shortness of breath, also known as angina. If a plaque of atheroma fractures it can cause a blood clot in the coronary artery, cutting off the blood supply to the heart muscle – this is known as a heart attack or myocardial infarction.

CABG surgery is an operation used to treat CHD. It uses blood vessels from another part of the body and connects them to blood vessels below the narrowed or blocked section to bypass – or 'get around' – it. The first successful CABG surgery was performed in 1961 in the USA [18]. During the rapid expansion of CABG that took place both internationally and in the UK during the late 1970s and 1980s, one of the main problems that emerged was the late degeneration and failure of the grafts leading to symptom recurrence. The BHF funded research to test different types of blood vessel grafts and different ways of harvesting them, with the view to understand the causes of graft failure and to find therapeutic approaches to improve the longevity of blood vessel grafts.

[a] https://www.bhf.org.uk/informationsupport/heart-matters-magazine/research/heart-lung-machine-in-surgery

[b] https://newsroom.heart.org/news/steps-outlined-to-reduce-the-risk-of-stroke-during-after-heart-surgery

a) Improving blood vessel graft harvesting and grafting

i. Improving vein graft harvesting

The saphenous vein, found in the leg, was the first commonly used bypass graft and still is. In the 1980s, Gianni Angelini, then a BHF funded clinical fellow in Cardiff who later became BHF Professor of Cardiac Surgery, started collaborating with Mr Iain Breckenridge and Dr Andrew Newby, who later became the BHF Chair of Vascular Cell Biology[a], on a long series of studies. They demonstrated that the solutions used and the technical care with which the saphenous vein was harvested were critical to reduce significant damage to the blood vessel wall. This included damage to the inner lining (the endothelium), and the muscular outer lining (the media) [19, 20], which could explain subsequent vein graft failure.

The team developed a pig model of vein to arterial bypass grafting which has been used widely for this type of vascular biology research. They tested a range of practical strategies to protect the vein at the time of harvesting and improve subsequent graft patency (i.e. the grafted vessel supports adequate blood flow) over the following months or years [20, 21]. At the time of harvesting, pressure distension is applied to test for leaks in the vein graft, which could ultimately damage the graft. In the preclinical model they demonstrated that a 'no-touch' technique, with reduced pressure distension when the vein was harvested and prepared, resulted in reduced post-surgical remodelling of the graft (also known as neointimal hyperplasia) and improved graft patency [22].

High pressure distension can also damage the fat surrounding the graft. In a recent clinical trial, Professor Angelini and colleagues tested whether reduced pressure distension and preserving the fat around the blood vessel could improve graft patency. The results published in 2021 showed that whilst there were some benefits to the low-pressure approach there was no obvious impact on neointimal hyperplasia after 12 months [23].

ii. Use of an external stent to support the vein graft

In 1996, Drs Mehta and Izzat working in Professor Angelini's group at the University of Bristol showed in a pig model that supporting the vein graft using extravascular stenting (i.e. placing the vein in a sterile polyester tube to reduce the possibility of it stretching or kinking after grafting), dramatically reduced the degree of neointimal hyperplasia [24]. Eventually this therapeutic approach was evaluated in a BHF-funded pilot study in humans led by Mr Gavin Murphy in Bristol (now BHF Professor of Cardiac Surgery in Leicester) in 2007. Unfortunately, it did not demonstrate a positive impact on neointimal hyperplasia and there were concerns with respect to its impact on graft patency [25]. However, a clinical trial by the National Institute for Health and Care research (NIHR) led by Professor David Taggart from the University of Oxford and testing a different type of external stent identified a significant therapeutic benefit [26, 27]. This remains an area of interest in terms of potential to improve the late outcome of coronary artery bypass grafting.

i. Testing different types of grafts

Most patients undergoing CABG have several narrowed areas in their coronary arteries, requiring more than one piece of 'bypass' vessel. CABG has evolved over the years and surgeons have been testing different types of grafts, especially comparing surgical outcomes when using a vein graft (e.g. saphenous vein) or arterial grafts (e.g. Internal Thoracic Mammary Artery (ITA) or Radial Artery (RA) graft). Artery grafts are thought to have a better long-term patency compared to vein grafts.

However, grafted vessels, particularly veins, can become blocked or diseased over time. This can lead to symptoms returning and the need for further treatment. That is why some surgeons are using two ITA grafts instead of one plus a vein graft in the hope of improving long-term outcome.

[a] https://alumni.bhf.org.uk/news/598912

But the benefits of double ITA versus single ITA plus vein were unclear. The BHF, in partnership with the Medical Research Council and the NIHR, funded the international Arterial Revascularisation Trial (ART) led by Professor David Taggart to find out more. The results of ART, published in 2019, did not demonstrate a survival difference at 10 years postoperatively [28] but nevertheless the detailed and comprehensive evaluation, the only randomized trial of its kind, continues to provide ongoing insights into the differences between these two approaches[a].

Members of the ART research team are now taking part in a new trial - the 'Randomization of Single vs Multiple Arterial Grafts', or 'ROMA' study [29]. This trial will recruit patients undergoing CABG from across the world. It aims to test more definitively whether using multiple artery grafts is a better approach for this surgery. In 2021, the BHF funded a further 5-year follow up (i.e. a total of 15 years) for ART, currently in progress.

b) Understanding graft failure to better prevent and treat it

i. Targeting the remodelling of the vein graft

Dr Andrew Newby with Dr Abigail Soyombo at the University of Cardiff developed an in vitro culture system for human saphenous vein which allowed further elucidation of a range of mechanisms relating to neointimal hyperplasia. Through these different approaches they identified the importance of matrix metalloproteinases (MMPs) in neointimal hyperplasia [30] and explored the potential of matrix metalloproteinase inhibitors as a therapeutic approach to reducing intimal hyperplasia.

Targeting matrix metalloproteinases became the focus of then BHF-funded lecturer Dr Andrew Baker, also working in Cardiff with Dr Newby before both joined Gianni Angelini in Bristol when Andrew Newby was appointed as a BHF Professor. Dr Baker developed expertise in adenoviral gene transfer that enabled over-expression of specific MMPs or their inhibitors in vascular cells. In 2000, the team showed for the first time in vivo that over-expression of TIMP-3 (Tissue Inhibitor of Metalloproteinases 3), driven by adenoviral infection of the isolated vein before surgery, could substantially reduce neointimal thickening of porcine saphenous veins grafted into carotid arteries for at least a month [31, 32]. The therapeutic benefit of this approach has continued to be investigated by Andrew Baker who moved to the University of Glasgow and is now BHF Professor of Translational Cardiovascular Sciences in Edinburgh. In 2012, while in Glasgow, Professor Baker and colleagues were funded by the BHF and the Medical Research Council to lead a clinical trial to test the long-term value of TIMP overexpression to prevent failure of saphenous vein coronary bypass grafts due to progressive intimal thickening and thrombosis[b]. Despite substantial obstacles in clinical manufacture of the adenovirus vector and COVID-related delays, the team are now filing regulatory approvals to initiate a first-in-human study in early 2023 at the Golden Jubilee National Hospital in Glasgow.

Despite a great deal of knowledge relating to molecular events leading to vein graft failure, limited therapies targeting neointimal hyperplasia have emerged with the exception of lipid lowering and antiplatelet drugs (i.e. Statin, Aspirin, Clopidogrel). However, these fail to target the root cause(s) of neointima formation. The BHF continues to fund research across the UK to identify potential therapeutic targets and develop innovative therapies to prevent neointimal hyperplasia and vein graft failure.

ii. A risk score to predict vein graft failure

The BHF funded Professor Charalambos Antoniades and colleagues at the University of Oxford to conduct an individual patient data meta-analysis, to identify an association of factors influencing the early failure of vein grafts (including clinical, anatomical, and operative characteristics). The team developed the SAFINOUS risk score and used it retrospectively on a validation cohort where it

[a] https://www.bhf.org.uk/what-we-do/our-research/impact-of-clinical-trials/art-trial
[b] https://www.gla.ac.uk/news/archiveofnews/2011/august/headline_208353_en.html

was successful in predicting early graft failure in around 70% of cases [33]. This risk score could be used to identify high-risk individuals who could benefit from more intensive treatments to prevent or delay vein graft failure.

c) Developing and testing new CABG surgery techniques

iii. Development of off-pump CABG

Conventional bypass surgery involves stopping the heart beating, so that the surgeon can operate on a heart that isn't moving and full of blood. The patient's blood is diverted to a heart-lung machine and after the grafts have been constructed, the heart is restarted, and the heart-lung machine is disconnected. However, stopping the heart beating and diverting blood supply into a machine is a traumatic process for the body which can be associated with serious post-operative complications. In the late 1990s and early 2000s, Professor Angelini and his team pioneered a technique to keep the heart beating during CABG surgery called 'off-pump CABG'.

The team faced several hurdles to overcome to make "beating heart" surgery possible. One was to find a way to stop the specific section of the heart the surgeon is operating on from moving. The idea of using a stabiliser device came to Professor Angelini in 1996[a]. He developed his own design for such a device and devoted three years to its development. It was made with stainless steel, inexpensive (cost about £800), and could be reused hundreds of times. Although stabilisers are now commercially available and sold by many medical manufacturers, prototypes like Professor Angelini's stabiliser helped paved the way for the sophisticated designs used today.

With funding from the BHF from 1997 to 2005, Professor Angelini's team conducted two trials comparing the off-pump technique with the standard technique. Patients who had off-pump surgery suffered less damage to their heart muscle, experienced less bleeding and need for transfusion, and had fewer episodes of heart rhythm disturbance immediately after surgery. The research suggested they may also be less likely to develop certain serious complications after surgery, such as a stroke. Their stay in hospital whilst recovering was also shorter [34].

Since these early trials, there have been several larger studies conducted across different hospitals comparing the two techniques, confirming the short-term benefits. There are some drawbacks, in particular the fact that off-pump surgery is more difficult to perform and if emergency surgery is required, there may not be ready access to a surgeon with the training required. But BHF-funded research has shown that, when performed by experienced surgeons in centres with the right infrastructure, off-pump surgery is a safe alternative to conventional surgery, both for higher-risk and lower-risk patients, and is associated with reduced complications both in the short and long term [35].

The pros and cons of performing off-pump bypass surgery are still fiercely debated by cardiac surgeons. Currently, off-pump bypass surgery is still a specialised practice. With more surgeons specifically trained to perform the technique and with technological advances, such as robot-assisted surgery, this procedure has the potential to be more widely adopted.

iv. Comparison of CABG with non-invasive percutaneous coronary intervention

Percutaneous coronary intervention (PCI), also known as coronary angioplasty with or without stenting, was first performed in 1977. PCI is a non-surgical intervention where a catheter is inserted via an arm or leg artery and advanced to the site of the blocked coronary artery. A balloon is inflated to open the blocked vessel (this procedure is called angioplasty) and a stent is inserted to hold the blood vessel open.

[a] https://www.bhf.org.uk/what-we-do/our-research/research-successes/beating-heart-surgery

With further developments in the field of PCI, it became important to understand when and how to use CABG or PCI to get the best possible outcomes for patients.

In the late 1980s/early 1990s, the BHF funded trials by Professor Edward Sowton at King's College London and Professor John Hampton at the University of Nottingham to compare CABG with PCI in different clinical settings [36-38]. The Randomized Intervention Treatment of Angina (RITA) trial compared patient outcomes and health service cost of CABG and PCI but didn't highlight any differences in long-term patient outcomes or long-term healthcare costs.

In the early 2000s, the BHF supported the 'Stent or Surgery' trial led by Dr Rod Stables at the Royal Brompton Hospital in London. This trial showed that long-term mortality was similar after CABG and PCI in most patient subgroups; however, CABG was associated with lower mortality in patients with diabetes and patients aged 65 years or older [39].

Findings from these landmark trials have influenced UK and international clinical guidelines for the management of stable angina and the use of PCI [40].

v. Minimally invasive CABG technique

In 1996, surgeon Antonio Calafiore and colleagues in Italy developed a minimally invasive direct coronary artery bypass (MIDCAB) grafting technique via a mini thoracotomy, an incision between the ribs to see and reach organs in the chest, including the heart [41]. This was initially designed to be an alternative to a second round of open-heart surgery in suitable patients. The benefits of MIDCAB surgery versus PCI were evaluated in a multicentre trial run by Professor Barnaby Reeves in Bristol in a cohort of patients who were suitable for either. In 2004, the trial reported that the new surgical approach was the equivalent in terms of early and mid-term outcomes, but was more expensive and therefore could not be recommended for routine use [42]. However, it confirmed the safety of MIDCAB, a technique that has now found a place in the surgical armamentarium in the UK.

While MIDCAB has proven useful to treat single vessels, its application is more limited for multivessel disease. MIDCAB doesn't allow multiple revascularisation because of the inaccessibility of other arteries through the small chest incision; while the use of PCI remains limited to anatomically suitable lesions. Professors Angelini, Calafiore and colleagues in Bristol were the first to combine both MIDCAB and PCI simultaneously in so called hybrid coronary revascularisation [43]. Since then, further evaluations have tended to favour a staged approach to revascularisation with PCI and subsequent surgery via a MIDCAB done within 60 days. This hybrid approach could be favored for younger patients who will require further surgery at a later stage or for elderly patients for whom CPB is contraindicated. Although the prospects of this hybrid approach are promising, evidence of its benefits compared to conventional CABG or PCI are limited and have restricted its widespread use.

4) Heart valve replacement

a) The Ross procedure

One of the first BHF research grants in the early 1960s was awarded to a pioneer in heart valve replacement surgery, Mr Donald Ross. The grant was to fund his efforts to improve the safety of an innovative operation using human heart valves (known as homografts) to replace diseased aortic valves, not only evaluating their early haemodynamic performance but also their longer-term durability and the different approaches to their preservation.

In 1967, Ross performed a world-first operation, that would come to bear his name, to treat people with a faulty aortic valve. It involved not one but two valve replacements. First the faulty aortic valve was removed and the patient's own healthy pulmonary valve (autograft) was used to replace it. A preserved valve from a deceased donor was placed in the position originally occupied by the patient's pulmonary valve. The thinking at the time was that the original healthy pulmonary valve would have the best chance of withstanding the high-pressure that the aortic valve faces with each

heartbeat. This procedure was a significant development in heart valve surgery, and many patients went on to live for 20 years or more. The procedure is still used by some surgeons specialised in the technique today, especially for treating young adults as well as infants and children born with congenital heart disease.

b) What type of heart valve replacement and when

The 1960s and 1970s were a time of innovation for heart valve replacement technology. The first successful artificial valve was inserted in 1960, and valves with similar designs have now been in use for over 40 years. Throughout this period new types of artificial valves and biological valves (using human, pig or cow tissue) have been developed and trialled in humans.

Faced with growing options to choose from, it became important to understand more about how these valves were being used and what were the outcomes for the patients. The BHF supported the Edinburgh Heart Valve study, set up in the 1970s by BHF Professor David Wheatley, and the UK Valve Registry, started in the 1980s by BHF Professor Ken Taylor. These studies collected information on how many patients were having valve surgery, what type of valve was being used (artificial or biological valve), and how successful the procedures were. They provided vital information to help surgeons and patients make informed treatment decisions, for example to choose between biological and artificial valves. Another important finding was that older patients, in their 80s or even early 90s, could still benefit from valve replacement surgery.

Between 1992 and 1996, cardiac surgeon Alan Bryan working with BHF Professor Angelini at the University of Bristol conducted a randomized comparison of two of the most commonly implanted mechanical heart valves over a 10-year period after the surgery, which remains the only such study in the world [44]. At the time, there were concerns around whether in the long term there would be differences in the clinical performance of these two types of valves and the risk of complications. The study reported no significant differences in the clinical outcomes between the two valves.

After a heart attack, some patients are at increased risk of heart failure because of a leak in the mitral valve of the heart (which separates the two chambers in the heart called the left atrium and left ventricle), also known as mitral valve regurgitation. Many patients who have had a heart attack undergo CABG surgery. Professor John Pepper and colleagues at the Royal Brompton Hospital in London tested whether repairing the leaky valve during this operation would enhance heart function and improve recovery after a heart attack. The team compared the impact of repair of the mitral valve and CABG against CABG alone. Ultimately the outcome was very clear, and the trial was discontinued after a year because the benefits of mitral valve surgery at the time of the CABG surgery were clearly demonstrable, with final results reported in 2012 [45]. This study had a significant impact on decision making in a controversial area and has influenced international guidelines for the decision pathway on the management of mitral regurgitation [46].

A major study related to valve replacement surgery currently underway, funded by the BHF, which may have a significant impact on UK surgical practice.

The study, led by Professor Gerry McCann in Leicester, is looking at the place of aortic valve replacement in patients with severe but asymptomatic aortic stenosis[a]. Aortic stenosis (AS) is a common condition where the aortic valve becomes progressively narrowed. It can take years for people with severe aortic stenosis to develop symptoms, which include shortness of breath and chest pain. Some may never develop symptoms, but even those without symptoms may still be at risk of heart failure or sudden death. When people have symptoms, surgery to replace the aortic valve is a good treatment but, as with any major surgery, there is a risk of complications and a long recovery process. Doctors therefore consider whether they should only offer surgery to those with

[a] https://www.bhf.org.uk/research-projects/the-early-surgery-in-severe-asymptomatic-aortic-stenosis-trial-easyas

severe aortic stenosis or wait until symptoms develop to avoid unnecessary major surgery. There is currently no evidence on how early patients with aortic stenosis should be treated. Professor McCann's international trial aims to find out whether having early surgery reduces the risk of death or hospitalisation from heart failure due to AS. The results could lead to new clinical guidance on how best to treat people with the condition.

c) The quest for the next generation of heart valve replacements

Currently faulty heart valves are replaced with either an artificial valve or a biological valve. Both types have pros and cons. An artificial valve, often referred as a mechanical valve, is long-lasting but comes with a higher risk of blood clots forming on the valve surface, which means the patient must take lifelong blood-thinning drugs. This medication prevents clots forming on the valve, but also increases the risk of serious bleeding. Biological valves are made from pig or cow tissue, and usually mean that blood-thinning drugs are not needed. But these valves don't last as long, and the patient may face further surgery years later.

There have been significant efforts by researchers in the UK supported by the BHF to design, develop and test new heart valves. These were led by BHF Professor David Wheatley's group in Glasgow from the 1980s where a polyurethane heart valve was developed and tested in animals[a]. The principle behind this initiative was to design a synthetic heart valve which did not require anticoagulation, could be mass produced and was durable [47, 48]. Unfortunately, despite extensive partnership with a UK valve company (Aortech) clinical trials were not successful to support widespread implantation.

In 2020, Professor Geoff Moggridge at the University of Cambridge, Professor Raimondo Ascione at the University of Bristol and colleagues described their work on a new artificial valve – called the PoliValve – which is designed to closely resemble a natural heart valve [49]. It combines strength with flexibility, and its use would not require blood-thinning drugs. While further refinement and testing is needed before this valve can be used in patients, the PoliValve has the potential to be a big step forward for the thousands of patients who require valve replacement surgery.

Babies born with a congenital heart disease often need valve replacement surgery using replacement grafts. Despite being lifesaving, these replacement grafts are not live tissues. This means they do not grow with the child and degenerate and fail in a few months or years. For these reasons, many children come back for more open-heart surgical operations with all the risks associated. In 2021, the BHF funded Professor Massimo Caputo and colleagues' work at the University of Bristol [50]. They are aiming to develop tissue engineered living vascular structures, in the form of conduits and patches, using stem cells isolated from the baby's umbilical cord, neonatal thymus and neonatal heart. These grafts have the potential to adapt to and grow with the child's heart. Once a clinical grade version of the new graft is created, the team will be ready to test it in patients. If successful, this study could reduce the need for additional and high-risk surgical re-intervention. This would remarkably improve the quality of life of many children undergoing cardiac surgery for correction of congenital heart disease.

[a] https://alumni.bhf.org.uk/news/478440

5) Heart transplantation

Since its inception, the BHF has funded research into heart transplantation - pre-dating even the world's first heart transplant in 1967.

a) Heart transplantation pioneers

In 1968, heart surgeon Mr Donald Ross performed the UK's first, and world's 10th heart transplant [51] following five years of BHF-funded research into heart transplant surgery techniques in preclinical models.

In the 1970s, BHF-funded Professor David Hearse made a major breakthrough, developing a fluid called 'St Thomas 1' as a means of stopping and cooling the heart and reducing oxygen consumption (also called cardioplegia, further discussed in section 6.a.i). It has been used in hospitals all over the world and is still used in the UK today. The solution was also found to play a key role in heart transplantation, preserving donor hearts for longer than previously possible.

b) Detecting and controlling rejection of the donor heart

Very early on, it was identified that rejection of the donor organ was the major challenge of transplantation. This happens when the body's immune system recognises the new heart as foreign and attacks it, just as it would attack an infection. To prevent their new heart from being rejected, transplant recipients must take drugs to suppress their immune system for the rest of their lives.

Since the 1970s, the BHF has been funding research to fight organ rejection. This includes the work of world-renowned surgeon Mr (now Professor Sir) Magdi Yacoub (who later became BHF Professor of Cardiothoracic Surgery) at Harefield Hospital and Imperial College London to understand how and why the body rejects the donor organ and to test different regimens of immunosuppressant to decrease the risk of rejection [52]. This is a very large field of research, other groups working on tackling this challenge have included those of Profs Kathryn Wood in Oxford, Robert Lechler at Imperial College London, Andrew Bradley in Cambridge and Marlene Rose, working with Prof Yacoub at Harefield.

A late consequence of rejection is that the lining of the blood vessels of the donor heart – the "frontier" between donor and recipient, becomes thickened. This is known as cardiac allograft vasculopathy. The condition can cause the blood vessels supplying the heart to become narrowed, leading to impairment of the heart muscle. Dr Michael Burch at Great Ormond Street Hospital has looked in detail at the mechanisms of this process. Its detection in children can be difficult, and in collaboration with Dr Michael Griel at Kings College, the GOSH group have studied the use of MRI as a non-invasive approach for imaging the coronary arteries in paediatric heart transplant recipients [53]. This will allow closer follow-up and better prevention of coronary allograft vasculopathy in children.

The BHF has also been funding the work of BHF Professor Federica Marelli-Berg and colleagues at Queen Mary University of London, who are using an innovative approach to tackle heart transplant rejection. Her team is trying to 'hijack' the immune system and stop it attacking the transplanted heart. When immune cells are alerted to the donor heart, they travel through the body to reach it. The team discovered that to find their target, immune cells are armed with surface proteins that act like a GPS system, using the 'area code' for the heart to reach their destination. Blocking this 'navigation system' could lead to new treatments to reduce organ rejection [54].

The BHF has supported the work of Professor Giovanna Lombardi and colleagues at King's College London who have been investigating the role of a subset of immune cells called T regulatory cells (Tregs), that can suppress the immune response. They want to harness this function in a range of conditions, to stop the immune system from attacking healthy cells (like in autoimmune disease)

but also to prevent heart transplants being rejected. The team have isolated Treg cells from thymus tissue, which is usually discarded after a heart transplant. They grew the cells in the lab and showed that they retain their immunosuppressive activity. Their protocol allows them to produce enough cells to be used in the clinic in paediatric heart transplant patients [55]. A previous phase 1 clinical trial had shown the safety and feasibility of Treg infusion to promote immune tolerance [56]. The team are now conducting new studies to evaluate their efficacy. In 2019, Professor Lombardi, in partnership with six leading experts from King's College London, University College London and Hannover Medical School, founded the spin-out company Quell, to accelerate the development of engineered Treg cell therapies. The company attracted substantial investment from the private sector. In 2021, it raised a further $156 million to fund the clinical development of QEL-001. Patient recruitment for the LIBERATE trial began in 2022[a].

c) How to identify and optimise the donor heart

All successful heart transplantations depend on choosing the best hearts from donors to use. The late Prof Robert Bonser in Birmingham was supported by the BHF to perform definitive studies in the donor heart – a challenging environment. His team showed that measuring cardiac output and optimising the resistance of blood flow around the donor body was important to avoid excessive use of potentially damaging drugs. This includes norepinephrine, a drug known to be toxic to the heart but which was once the most commonly used vasoconstrictor agent in hypotensive organ donors. Norepinephrine is now recommended to be used sparingly in organ donors [57]. Professor Bonser and colleagues also showed that adding thyroid hormone, which was widely used then to the retrieval rate of donor heart and improve its function after transplantation, made no difference at all [58]. This change has now been accepted worldwide and thyroid hormone is no longer used for this purpose.

d) Increasing the number of children able to receive a heart transplant

Over the last 20 years, doctors have increased the number of organs available to children needing a transplant by using hearts from donors with different ABO blood types from theirs. This exploits the fact that younger children have low or non-existent levels of ABO antibodies. If some antibodies are present, the child's blood is slowly replaced with a blood type that matches the donated heart. This means the procedure is limited to smaller children who are typically 4 years old or younger, and older children must wait for a heart that matches their blood type. The BHF funded Dr Richard Issitt and colleagues at Great Ormond Street Hospital to test a blood filtering device that removes mismatched antibodies in the blood that can lead to transplant rejection. The filter is added into the heart and lung machine used to support the child during surgery. This consequently halves the amount of donated blood required during the transplant itself and in the intensive care unit afterwards, allowing larger, older children to have an 'incompatible' transplant – making them more likely to be matched with a suitable heart. All of the children who had a transplant using the new device survived, there was no need for re-transplantation and there was no difference in the length of hospital stay 6-12 months after the transplant [59].

[a] https://quell-tx.com/quell-therapeutics-raises-156-million-in-oversubscribed-series-b-financing-to-advance-its-pioneering-multi-modular-engineered-t-regulatory-treg-cell-therapy-pipeline-and-platform/

6) Perioperative care

a) Myocardial protection

Damage to the heart muscle, also called myocardial injury, sustained during cardiac surgery is associated with worse short-term and long-term clinical outcomes. The UK has consistently been at the center of research efforts to develop more effective methods of protecting the myocardium during cardiac surgery. Early methods of myocardial protection in the late 1950s and early 1960s developed by Drs Dennis Melrose and Hugh Bentall, who became the UK's first professor of cardiothoracic surgery at Hammersmith hospital, included the use of potassium citrate to induce elective cardiac arrest [60]. However, this method was later abandoned due to myocardial cell damage. Since then, BHF-funded studies described below have advanced this field from improving cardioplegia techniques to understanding the role of pre- and post-conditioning to protect the heart from injury.

i. Cardioplegic solution

Cardioplegia is a pharmacological therapy administered during cardiac surgery to temporarily arrest the heart.

Work by BHF Professor David Hearse and cardiac surgeon Mark Braimbridge was instrumental in advancing cardioplegia. Their research efforts which commenced in the mid-1970s, and were supported by the BHF, resulted in the development of a crystalloid cardioplegic solution (St Thomas's 1) which was highly effective and widely used in cardiac surgery [61]. By the mid 1980's this collaborative effort resulted in the further development of an improved cardioplegic solution (St Thomas's 2- "Plegisol") [62] which has transformed cardiac surgery, particularly CABG surgery, during a period of rapid expansion. It is a practical advance that was cheap, simple and remarkably effective.

During the 1980s further studies evaluated the impacts of blood cardioplegia and a range of different formulations, timings and modes of delivery including retrograde administration, delivered through a catheter placed through the right atrium into the coronary sinus, and "hot shot" warm reperfusion cardioplegia, the administration of warm perfusate.

Dr Massimo Caputo at the University of Bristol (now BHF Professor of Congenital Heart Surgery there), explored the effectiveness of different concentrations of magnesium supplementation to intermittent warm blood cardioplegia and its impact on the efficacy of myocardial protection [63]. The research suggested that magnesium could reduce myocardial injury in patients undergoing CABG. Dr Caputo and colleagues tested their findings in a clinical trial which showed that adding magnesium to cardioplegia did not reduce the frequency of postoperative atrial fibrillation in patients undergoing CABG but may reduce cardiac injury [64]. However, a meta-analysis published in 2015 showed that the advantage of magnesium-supplemented cardioplegia were unconvincing based on current evidence [65].

The BHF is currently funding a pilot trial led by paediatric surgeon Mr Nigel Drury at the University of Birmingham to compare how well two types of cardioplegia protect the heart during heart surgery in children[a]. St Thomas' solution is commonly used in adults and children undergoing open heart surgery in the UK, while del Nido cardioplegia is commonly used in children in the US. There is evidence that del Nido cardioplegia may be better at reducing the effects of ischaemia-reperfusion injury (IRI) in young heart muscle. This pilot trial could provide the basis for carrying out a larger trial to provide an answer to which cardioplegia is best for this type of surgery and could result in heart surgery becoming even safer for children around the world.

[a] https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2021/december/new-clinical-trial-aims-to-improve-heart-protection-during-surgery-in-children

ii. Conditioning

Preconditioning refers to the ability of short periods of blood flow restriction (also called ischaemia) to make the myocardium more resistant to subsequent ischemic insult. The phenomenon has been recognised as a powerful mechanism to protect against myocardial ischemic injury caused by heart attacks. BHF funded studies by Professor Derek Yellon and Professor David Hearse aimed to further understand this phenomenon in the laboratory but also to understand whether it could be utilized for clinical benefit [66-69]. This work has provided important insights into the signalling pathways underlying myocardial protection. However, translation into the clinical setting has proved difficult.

In 1993 Professor Yellon demonstrated for the first time that repeated short episodes of ischaemia caused by brief aortic cross-clamping in patients before CABG protected the human myocardium [70].

Studies by Dr (now Professor) Derek Hausenloy and Professor Yellon at the Hatter Cardiovascular Institute at University College London (UCL) reviewed the role enzymes called survival kinases in mediating the cardioprotective effects of preconditioning and postconditioning [71]. In 2002, Professor Yellon's group described for the first time the reperfusion injury salvage kinase (RISK) pathway, while other international groups had identified the involvement of another pathway involving the adenosine molecule [72, 73].

Yellon's group then studied the prospect of pharmacological preconditioning using drugs targeting these pathways specifically. However, none of these methods were successful in protecting the heart.

Other BHF-funded research set out to identify the molecular mechanism underlying myocardial protection induced by ischaemia. Professor Michael Marber and colleagues at King's College London studied the role of an enzyme responsible for glycogen synthesis, called GSK-3. Inactivation of GSK-3 was proposed as the event integrating protective pathways initiated by preconditioning. The team investigated the role of inactivation of GSK-3 in both ischemic preconditioning and postconditioning. Their findings, based on a combination of genetic and pharmacological interventions, did not support the premise that GSK-3 inhibition is essential to pre- or post-conditioning of isolated mouse hearts, suggesting that the inhibition of this enzyme is unlikely to be the key determinant of cardioprotective signalling [74]. BHF funded studies from Professors Yellon and Robert Bonser at the University of Birmingham evaluated whether remote ischaemic preconditioning (RIPC) had a part to play in myocardial protection [75]. RIPC is defined as brief episodes of ischemia at a remote site before subsequent prolonged ischemia/reperfusion injury of the target organ. Cycles of forearm ischaemia and reperfusion by the inflation of a blood pressure cuff for brief periods is the preferred method.

In 2007, Professor Yellon and colleagues became the first group to demonstrate a clinically beneficial effect on myocardial protection as a consequence of RIPC [76]. The study shown that RIPC, mediated by transient upper limb ischaemia can reduce troponin T in the perioperative period in adults undergoing coronary artery bypass graft surgery. Troponin T is a marker of myocardial injury and is associated with poor short-term and long-term clinical outcomes after surgery.

Between 2011 and 2014, a clinical trial led by Professor Hausenloy and colleagues funded by the BHF aimed tested whether RIPC before CABG could improve clinical outcomes (the ERICCA trial[a]). The study did not show any evidence of protection after RIPC. Heart and circulatory complications, duration of stay in the intensive care unit and hospital, quality of life and all the other outcomes studied were similar with or without the preconditioning in CABG patients. This was the first trial of

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

its kind and led to a later study (ERIC-PPCI trial[a]) carried out by Professors Hausenloy and Yellon at UCL, Professor Rajesh Kharbanda at the University of Oxford and Professor Tim Clayton at London School of Hygiene and Tropical Medicine. This time, the team questioned whether RIPC protected against injury from primary percutaneous coronary intervention (PPCI). The ERIC-PPCI trial ran from 2013-2018 and the results of the trial, which involved 26 UK hospitals, were combined with another trial (CONDI-2) taking place across Denmark, Spain and Serbia. The study did not show any evidence of protection after RIPC. Thus, despite good preclinical evidence for the ability of ischaemic conditioning to protect the heart, these trials have ruled out its value for clinical practice.

The possibility that blocking specific mechanisms shown to contribute to conditioning will be clinically beneficial is still being investigated.

b) Blood conservation

One of the most significant developments in perioperative management was the discovery by BHF Professor Ken Taylor and colleagues at Hammersmith Hospital in London that aprotinin (Trasylol™) was a powerful drug to reduce blood loss in cardiac surgery [9]. The use of this drug made a major difference to blood and blood product usage and overall mortality at the time of reoperative cardiac surgery particularly (a repeat operation for the same condition). It was also applied to other high risk situations including endocarditis, heart and lung transplantation and complex aortic surgery [77]. Following its successful introduction and ultimately widespread use, concerns were raised about its safety in the early 2000s [78]. However, after a period of concern this extremely valuable drug has been restored to its useful place of assisting in haemostasis in higher risk procedures [79].

The importance of blood conservation and the avoidance of unnecessary transfusion was identified by Mr Gavin Murphy and Professor Barney Reeves and colleagues at Bristol University as having a negative impact on survival after cardiac surgery. They subsequently considered whether a more stringent transfusion threshold (using a lower haemoglobin concentration as a threshold for transfusion) would result in better outcomes. However, in a randomized control prospective trial (TITRe2), no overall survival benefit was demonstrated [80].

c) Understanding and preventing the development of atrial fibrillation after cardiac surgery

Atrial fibrillation (AF), a type of abnormal heart rhythm, occurs in up to 40% of patients after cardiac surgery[b]. Atrial fibrillation can increase the risk of stroke. BHF researchers have sought to understand how AF develops after cardiac surgery, and how the risk of post-operative AF can be reduced.

The precise mechanisms which underly post-operative atrial fibrillation remains an area of intensive investigation. BHF funded research carried out by Professor Nicholas Peters at Imperial College London found that post-operative AF is associated with a pre-existing structural and electrical abnormality in human right atrial myocardium, offering a novel mechanism and manifestation of post-operative AF [81].

Work by Mr S Kolvekar at the University of Leicester examined whether the structure of the atrial coronary artery was related to the incidence of post operative AF. His work found that people who had evidence of obstructive disease (those that cause a narrowing of arteries) in the sinoatrial and atrioventricular nodal arteries, were more likely to develop AF following CABG. Those with a normal sinus rhythm following the surgery tended not to have signs of obstructive disease [82].

[a] https://www.bhf.org.uk/what-we-do/our-research/impact-of-clinical-trials/eric-ppci-trial
[b] https://newsroom.heart.org/news/steps-outlined-to-reduce-the-risk-of-stroke-during-after-heart-surgery

i. Reducing the risk of post-operative atrial fibrillation

To prevent the development of atrial fibrillation, efforts are made to maintain postoperative serum potassium levels, an ion important to keep the heart beating at the right pace, in the high-normal range. However, the efficacy of such treatment is unproven. The BHF is funding a clinical trial, the 'Tight K Study', led by Dr Ben O'Brien at Queen Mary's University London to test whether keeping blood potassium levels at a high normal level after heart surgery is necessary to prevent abnormal heart rhythms[a]. After carrying out a successful pilot trial [83], the team are now preparing for a larger trial involving over 1600 people, which is expected to report in 2025.

BHF Chair of Cardiovascular Medicine, Professor Barbara Casadei, and colleagues at the University of Oxford have been studying the anti-arrhythmic effect of statins and investigating whether they are beneficial in patients undergoing cardiac surgery [84, 85]. In 2016, a clinical trial supported by the BHF and led by Professor Casadei demonstrated that giving daily doses of statins for a few days before and after heart surgery does not prevent heart damage or atrial fibrillation [86]. The trial also found that statins increased the risk of postoperative kidney damage. This work has influenced clinical guidelines for the management of AF and for perioperative care of patients undergoing cardiac surgery, which now state that statins should not be started in people having cardiac surgery solely to prevent post-operative AF[b].

d) Development of new technology to plan surgery

i. Modelling of cardiovascular diseases to plan surgery

It is important for surgeons to have a clear understanding of the anatomy of the diseased heart to be able to plan and adapt the surgery to the needs of individual patients. BHF-funded researchers have been studying how 3D printed hearts could help personalise treatment. In 2007, BHF-funded Professor Andrew Taylor and his team at University College London were among the first in the UK to use 3D imaging and computer models to help doctors get a better understanding of an individual's heart [87]. MRI scans have been used to produce a 3D virtual or printed model of an individual patient's heart. These can be a valuable tool to help surgeons and cardiologists prepare for surgery and other procedures particularly in children and adults born with congenital heart disease. They can also help the patients and their families get a better understanding of their heart condition.

While 3D imaging technology can be very useful to plan surgeries, the main limitation is that it offers only static models or projections on a flat screen. Recently, the BHF funded Dr John Simpson and colleagues at King's College London who have developed a virtual reality system for 3D heart ultrasound[c]. Surgeons have indicated it is better than conventional imaging when used to identify abnormal heart valves before they need replacing or repairing. In this project, Dr Simpson will expand the system so that it includes multiple imaging methods. His aim is to 'immerse' doctors into a virtual reality heart to 'road test' devices before surgery and allow clinical teams from several locations to plan care and make joint clinical decisions more easily. This work could lead to a new technology that will help doctors better understand the complex pathology underlying congenital heart disease whilst also improving their ability to plan procedures.

[a] https://www.lshtm.ac.uk/sites/default/files/2021-04/tight-k-trial-protocol.pdf
[b] https://www.nice.org.uk/guidance/ng196/chapter/Recommendations#preventing-and-managing-postoperative-atrial-fibrillation
[c] https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2022/february/new-virtual-reality-technology-to-repair-hearts

ii. Improving risk prediction for cardiac surgery

In tandem with research efforts the specialty has an enviable record of collecting and presenting the results of cardiac surgical procedures over many years. Sir Terence English developed the UK Cardiac Surgical Register in the late 1970s to enable centres to compare their outcomes and set practice standards. This was largely voluntary but provided useful information. A series of concerns, particularly around paediatric cardiac surgery in 2001, led to the evolution of this initiative into a comprehensive, risk adjusted record of all cardiac surgery activity in the UK with its main focus on mortality. Cardiac surgery has led the way in making such data available to the public and has set standards of professional practice that have provided a template for other specialties to follow.

People who require open heart surgery must be informed about the risks related to the operation. Heart surgeons in the UK calculate the risk using a mathematical model called EuroSCORE [88]. However, this model is no longer considered to be accurate in the UK, due to improvements in anaesthetics, surgical and post-operative care. EuroSCORE tends to overestimate the risk of death, which means patients or surgeons may choose not to go ahead with surgery that in reality would have a good chance of success. In 2011, a new score (EuroSCORE II) [89] was developed in an attempt to improve risk prediction, however, challenges still remain and work continues in this area to improve risk stratification.

In 2020, the BHF and the Alan Turing Institute funded Professor Angelini and Professor Chris Holmes, a statistician at the University of Oxford, to lead a team of doctors and data scientists to improve risk prediction in people having heart surgery. The team will apply machine learning to a large dataset of all patients undergoing major heart surgery in the UK to create an improved risk prediction score. This could ultimately help surgeons better identify patients who are likely to have successful heart surgery.

iii. Anaesthesia

While improving mortality and morbidity associated with cardiovascular surgery has been a key focus since the 1980s, more consideration is now given to improving quality of recovery for patients undergoing surgery. Anaesthesia is receiving increasing attention from cardiac surgeons and anesthetists looking into ways to improve recovery.

Professor Caputo and colleagues were supported by the BHF to undertake a study of the impact of thoracic epidural anaesthesia, in addition to general anaesthesia, in the context of off-pump CABG surgery. In 2011 they reported demonstrable improvements in length of ventilation, hospital stay, blood usage and risk of supraventricular arrhythmias. However, this technique did not alter the risk of perioperative myocardial damage [90]. This field has been extensively researched, with divergent findings. A Cochrane review published in 2019, analysing the results of 69 trials, including the one led by Professor Caputo, concluded that ‘epidural analgesia may reduce the risk of myocardial infarction, respiratory depression, and atrial fibrillation/atrial flutter, as well as the duration of tracheal intubation and pain, in adults undergoing cardiac surgery [91]. There may be little or no difference in mortality, pneumonia, and epidural haematoma, and effects on cerebrovascular accident are uncertain.

7) Paediatric cardiovascular surgery

As emphasised in the account of cardiac surgery in adults, the BHF has been in existence almost as long as surgical correction has been possible for most cases. This fact is particularly pertinent for the correction of congenital cardiac defects. There was little possible before the development of the cardiopulmonary bypass machine that made it possible to stop the heart, granting the cardiac

surgeon access to the multiple lesions that can be found within the heart in consequence of its abnormal development.

Paediatric cardiac surgeons are well recognised for their ingenuity, and the ability to develop new procedures to repair the abnormalities found once the heart has been opened.

a) Developing a coding system for congenital abnormalities

BHF support has helped to establish the UK as a leader in paediatric cardiac surgery. This can be evidenced by the National Institute for Cardiovascular Outcomes Research (NICOR)[a], which grew from the United Kingdom Congenital Cardiac Audit Database. This can be traced back to a BHF grant supporting Mr Jaroslav Stark of Great Ormond Street Children's Hospital in the 1970s, who recognised the need for surgeons to be able to code the abnormalities on which they were operating in simple fashion. Subsequent work carried out at the Royal Brompton Hospital expanded this concept to produce a more detailed coding system. This, in turn, has evolved to become the International Paediatric Congenital Cardiac Code [92]. This code will now become the cardiac component of the eleventh iteration of the International Classification of Disease.

The BHF funded several researchers who contributed to that work, including Professor John Deanfield (former BHF Professor of Paediatric Cardiology at Great Ormond Street Hospital), Professor Robert Anderson (former BHF Professor of Paediatric Cardiac Morphology at the Royal Brompton Hospital before transferring to Great Ormond Street for the final years of his tenure), as well as consultants still in activity and Dr Kate Brown (Great Ormond Street Hospital) and Dr Rodney Franklin (Royal Brompton Hospital).

b) Mapping congenital cardiac malformations

The success of surgeons in correcting the abnormalities that confront them is greatly enhanced by prior knowledge of the likely complexity of the lesions. The improvements made over the past decades, therefore, also reflect the ability of paediatric cardiologists to make accurate preoperative assessments of the underlying anatomy. With BHF support, Professor Anderson was able to describe virtually all the different holes and narrowings found within the malformed heart. To this end, he worked initially in close collaboration with Professor Fergus Macartney, then BHF Professor of Paediatric Cardiology at Great Ormond Street Hospital. Together, they pioneered the initial assessments of the various defects using cross-sectional echocardiography. This permitted Professor Anderson to combine these findings with his research into the electrical wiring system of the heart [93, 94]. Taken together, this made it possible to describe the landmarks that could be used by the operating surgeon to avoid these crucial small areas within the heart, where one stitch placed incorrectly could have catastrophic consequences. These initial studies are now being taken further by Professor John Simpson and his team who are assessing the ability to reveal these features in advance of the operation by means of virtual reality. The BHF also supported Dr Lindsey Allan to investigate the potential role of echocardiography to reveal the details of the congenitally malformed heart prior to birth [95]. Dr Allan was one of the very first to show that the technique was able to permit accurate prenatal diagnosis. She subsequently became BHF Professor for a short period of time (1992-1993), before moving to the US where she continued her research. The success of this research, initially funded by the BHF, now makes it possible for mothers carrying foetuses with severe cardiac malformations to be delivered at the hospital where surgery can immediately be performed, contributing in no small part to the huge advances already described.

[a] https://www.nicor.org.uk/

c) International collaboration in paediatric cardiac surgery

With the UK being world leading in the field of paediatric surgery, the BHF contributed to the initial training of several now world-renowned international paediatric surgeons, including Dr Andrew Redington, who initially collaborated strongly with BHF Professors Anderson and Deanfield before moving first to Toronto, and then to Cincinnati [96]. He, in turn, nurtured Dr Daniel Penny, who moved first to Melbourne, and then to Houston, and also Dr Lara Shekerdamian, who received an initial grant from the BHF before moving also to Melbourne and Houston, where she has recently been appointed Professor of Paediatrics.

The BHF supported multiple national, and three international, meetings to allow researchers and clinicians at the cutting edge of surgical developments, along with those promoting the ancillary skills required to achieve optimal success, to share their findings and expertise and prompt new collaborations. The proceedings of each of the international meetings were published as successful books, again made possible with BHF support.

d) The Fontan Procedure: Total cavopulmonary connection

The Fontan procedure is a procedure used in children who lack two fully developed ventricles. The surgery involves disconnecting the inferior vena cava, a large vein that carries deoxygenated blood from the lower body and attaching it to the pulmonary artery. After this operation, all deoxygenated blood from the body goes to the lungs without passing through the heart. Its introduction was the result of a flurry of experimental and clinical research that started in the 1940s. Since then, there have been a range of modifications to the operation to increase patient outcomes.

The work of Dr Philip Kilner and Professor Marc de Leval at University College London, supported by the BHF, led to improved understanding of the Fontan procedure using in vitro modelling and computational fluid dynamics. This led to the development of the total cavopulmonary connection (TCPC), sometimes referred to as the de Leval operation [97]. The Fontan procedure using TCPC is the most common procedure performed to treat congenital cardiac defects not amendable to biventricular repair (creating two functioning ventricles in a single procedure) [98].

e) Role of human factors in surgical outcomes

Professor de Leval was also supported by the BHF to study the role of human factors on surgical outcomes, focusing on a series of 243 neonatal arterial switch operations [99]. The arterial switch is a procedure that corrects transposition of the great arteries, a birth defect of the heart where the main pulmonary artery and the aorta are switched in position. By studying the influence of human factors, which included organizational, team, situational, and personal factors, Professor de Leval aimed to help physicians to understand adverse events and establish ways to prevent them. The study highlighted the role of human factors on surgical outcomes. It supported the suggestion that human factors should be incorporated in risk factor analysis. It also emphasized the need for more research in human factors in health care organizations.

f) Caring for congenital heart disease survivors

Advances in cardiovascular surgery, many of which are set out in this report, have meant that the number of adults who are surviving the heart conditions that they were born with is rising. Professor Jane Somerville at the Royal Brompton Hospital was one of the first people to recognize the importance of caring for the growing number of adult survivors of congenital heart disease. Professor Somerville developed the concept of 'GUCH' - grown-up congenital heart disease – and pioneered GUCH care in the UK and Europe. The BHF funded Professor Somerville to create a follow-up system for survivors of congenital heart disease to identify which factors make a difference to their long-term survival[a].

8) Conclusion

The support of the BHF has aided the development of cardiovascular surgery over the last 60 years. From the development of the technology and equipment required to support the heart during surgery to improving risk prediction in people having heart surgery, the BHF has transformed modern cardiac surgery into the routine and safe procedures that are undertaken today.

Looking ahead, advances in technology will lead to changes for the practice of cardiac surgery with more focus towards alternative or less invasive treatment. The development of advanced therapeutics to repair and regenerate heart tissue could help to revolutionise the field in the future, by preventing or delaying the need for heart surgery or improving patient outcomes after surgery. The BHF is playing a part in the revolution of cardiac surgery, supporting new ideas and training the next generation of medical professionals to ensure those needing heart surgery have the best possible outcomes.

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