British Heart Foundation

Lungs under pressure

Impact of British Heart Foundation support for pulmonary hypertension research

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This review was led by Professor Allan Lawrie, BHF Senior Fellow at the University of Sheffield

Message from our Medical Director

At the British Heart Foundation (BHF), we fund research to save and improve the lives of the millions of people living with or at risk of heart and circulatory diseases, in the UK and worldwide. We focus our efforts on supporting underpinning research and turning discoveries into lifesaving medical advances.

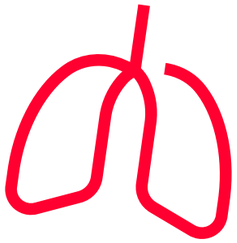
Working with research leaders, we are producing a series of compelling reviews that articulate the impact arising from the support of the BHF in specific fields of research, from the generation of new knowledge all the way to improving patients' lives.

The following pages illustrate the lasting impact of our research funding and some of the key players who made the breakthroughs, leading to better diagnosis, treatment and care of patients with heart and circulatory diseases. None of these achievements could have been realised without the generosity and dedication of our supporters, and the passion and perseverance of our researchers.

I hope they inspire you as much as they inspire me.

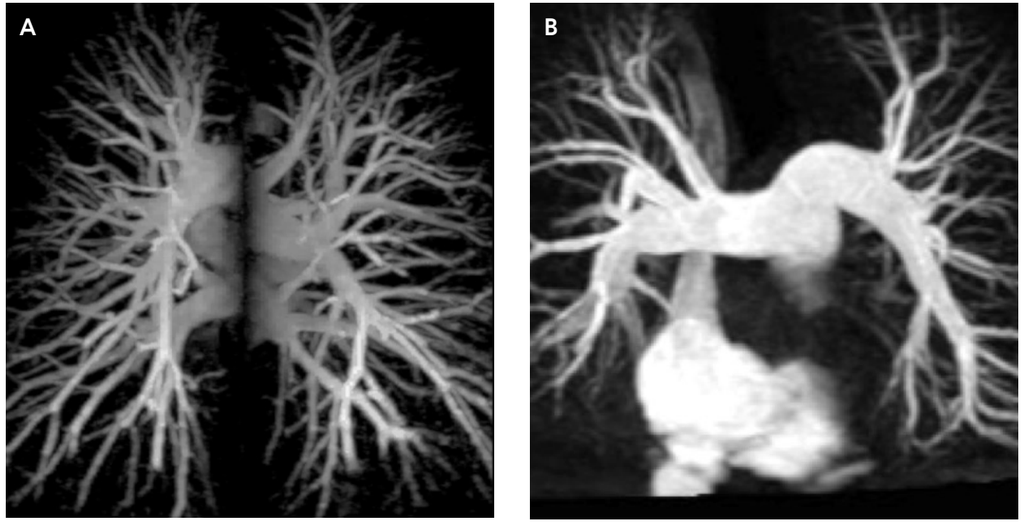
Professor Sir Nilesh Samani,
Medical Director, British Heart Foundation

What is pulmonary hypertension?



Pulmonary hypertension (PH) is a potentially life-threatening condition caused by high blood pressure in the arteries of the lungs. This high pressure can be caused by several different pathophysiological factors. PH is classified into five main groups based on their causes.
The present review focuses on the two groups described below:

Pulmonary arterial hypertension (PAH) (Group 1)	PAH where the increase in pulmonary artery pressure is driven by a progressive remodelling of the small pulmonary arteries. Subgroups of PAH include: • Idiopathic form of PAH where cause is unknown • Inherited form of PAH • PAH developing as a complication of congenital heart disease • Persistent pulmonary hypertension of the newborn (PPHN)
PH due to pulmonary artery obstruction (Group 4)	PH due to pulmonary artery obstruction such as chronic thromboembolic PH (CTEPH) where blood clots block arterioles and arteries reducing blood flow.



CT pulmonary angiogram of lung blood vessels

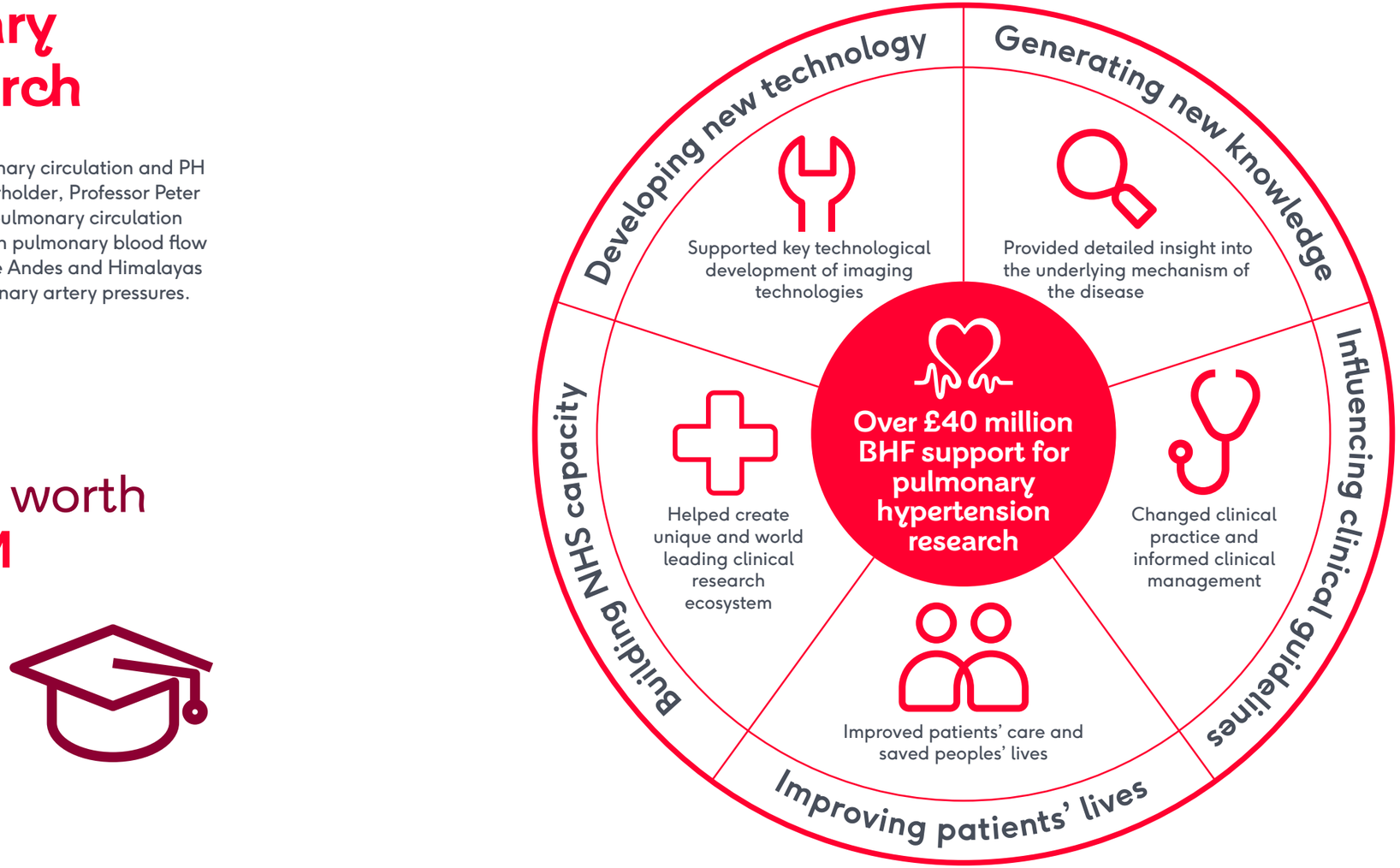
The blood vessel that runs from the heart then branches into the left and right lung is called the pulmonary artery. During a CT pulmonary angiogram, a dye is injected into a vein in the arm which travels to the pulmonary arteries. This dye makes the arteries appear bright and white on the scan pictures. Picture A on the left represents the lung blood vessels of a healthy individual and on picture B from a patient with PAH, where peripheral arteries are narrowed, increasing the pressure inside the vessels, limiting the circulation of blood to the lungs.

Our support for pulmonary hypertension research

The BHF has supported research into the pulmonary circulation and PH since its creation in 1961. The very first BHF Chairholder, Professor Peter Harris, was appointed in 1966. His research on pulmonary circulation extended to determining how animal and human pulmonary blood flow adapted at high altitude, with expeditions to the Andes and Himalayas where low oxygen levels can lead to high pulmonary artery pressures.

Over **200 grants** worth more than **£40M**

Supporting the training of **>30 PhD students,** and the career development of **>20 fellows** and **3 BHF Professors**



Generating new knowledge

Over the last 60 years our understanding of the causes of PAH, CTEPH and PPHN has increased dramatically, thanks in part to BHF-funded research. The BHF funded ground-breaking discoveries, including:

- Unveiling the role of the nitric oxide pathway in the pathophysiology of PH and development of novel treatments targeting this pathway.
- Helping identify genetic modifications causing PAH, including mutations in the gene BMPR2 responsible for more than 70% of inherited forms of PAH.
- Contributing to understanding the biological mechanisms of PPHN.
- Identifying several promising targets for the development of novel treatments.
- Currently supporting more research to identify novel mechanisms involved in the development of group 1 and group 4 pulmonary hypertension.

Finding the gene(s) causing inherited pulmonary arterial hypertension

In the 1950s, many scientists started to describe how pulmonary arterial hypertension ran in families and realised that PAH can be inherited. But until 2000, no one knew which gene or genes were involved.

In 2000, BHF-funded research led by Professor Richard Trembath at the University of Leicester showed that mutations in the gene BMPR2 caused inherited PAH. Today, we know that mutations in this gene are responsible for around 70% of inherited cases of PAH.

In 2001, Professor Trembath and Dr Nick Morrell (now BHF Professor of Cardiopulmonary Medicine at the University of Cambridge) built on this work, showing how changes in BMPR2 affect the blood vessels in the lungs and lead to PAH. Since then, we have supported research that has shed more light on the role of BMPR2 in the development of PAH, as well as looking at how we can block these effects in order to stop or reverse the changes or damage caused by PAH.

In 2015, Professor Morrell and his team identified a molecule that can stop the harmful effects of this change in the BMPR2 gene. They showed that in mice, this treatment can reverse PAH. These results demonstrated the potential of targeting the effects of the BMPR2 gene mutation, in order to offer a new treatment for PAH. This work led to the creation of the spin-out company Morphogen-IX to develop new PAH treatments. The company aims to begin studies of these treatments in humans in 2022.

Developing new technology

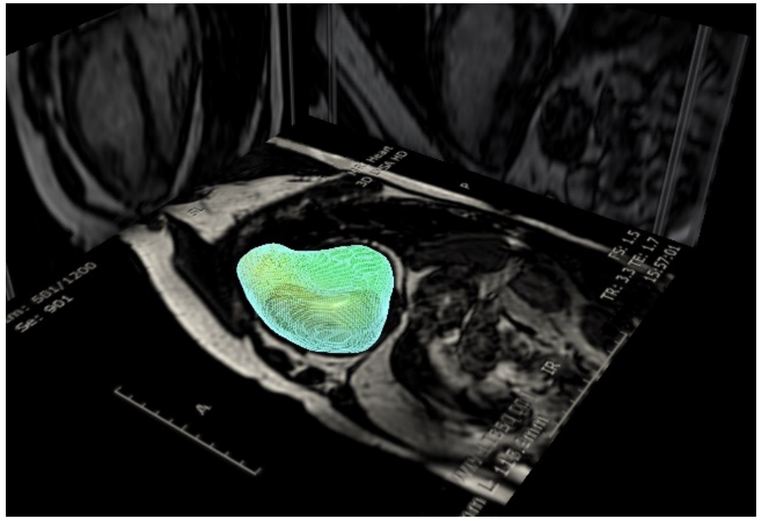
BHF-funded research has supported the development of methods and technology that have helped researchers and clinicians around the world to understand the biological mechanisms of PH and develop novel diagnostic tests, including:

- Developing pre-clinical models of PH to reproduce the disease in the lab, key to understanding disease processes and developing novel treatments and diagnostic tests.
- Helping build a national cohort of PH patients that is now linked to an international Consortium to create the world's largest datasets linking clinical and research data.
- Developing novel non-invasive imaging techniques that have the potential to replace the need for more invasive tests to diagnose and follow-up of both children and adults with PH.
- Using new machine learning and artificial intelligence approaches to improve diagnosis and guiding clinical decision making.

Predicting survival

In 2019, Professor Declan O'Regan and colleagues at Imperial College London, part-funded by the BHF, developed a computer program called 4D Survival. This program is based on machine learning – it accesses data from heart scans of hundreds of people with pulmonary hypertension, together with their health records to pinpoint the earliest signs of heart failure. This can then be used to interpret the scans of individual patients and predict the risk of dying from heart failure.

So far, the team have used the technology to predict the prognosis for more than 300 people with pulmonary hypertension. The program outperformed doctors, being able to correctly predict a patient's prognosis 75% of the time.



It is hoped that the new technology will help to identify which people are at risk of their condition worsening. This could make a big difference to the decisions that doctors make about how best to treat patients.

Heart MRI scans analysed with the computer program developed by Professor O'Regan

Influencing clinical practice

Because PH is a set of diseases with different causes, there are several targeted therapies available today, depending on what is causing the condition and the severity of the symptoms. Current treatments aim at slowing down the progression of the disease. In the most serious and advanced forms of PH, a lung transplant or heart-lung transplant may be needed. If the underlying cause is identified and treated early, it may be possible to prevent permanent damage to the pulmonary blood vessels and the heart. BHF-funded research has contributed to changing how we treat and manage people living with PH today by:

- Influencing clinical guidelines for the diagnosis, treatment and management of children and adults with PH.
- Contributing to the development of MRI-based diagnostic tools.
- Contributing to the development of drugs affecting the nitric oxide pathway – sildenafil and riociguat, that are used in the treatment of PAH and CTEPH.
- Supporting the refinement of heart and heart-lung transplantation surgery.

Targeting the nitric oxide pathway to treat pulmonary arterial hypertension

BHF-funded research by Professor Tim Higenbottam at the University of Cambridge in the late 1980s showed that having low levels of nitric oxide in the blood vessels of the lungs is a key factor in pulmonary hypertension. For the first time, they gave nitric oxide to people with severe PAH and showed that it reduced the blood pressure in their lungs.

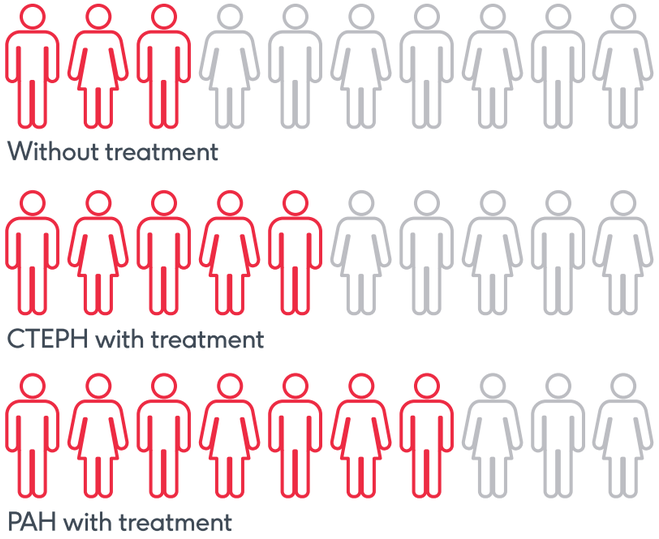
This pioneering work paved the way for the development of further treatments that target the way blood vessels release nitric oxide. As a result, new drugs called phosphodiesterase inhibitors were developed. One of the best known is sildenafil. In 2005, BHF-funded work by Professors Martin Wilkins and Lan Zhao at Imperial College London first demonstrated the benefits of using sildenafil to treat pulmonary hypertension.

Today, sildenafil and related drugs are the most prescribed medicines in the UK and worldwide for the treatment of PAH, helping to relieve breathlessness and improving lives.

Improving patients' lives

PH is a life-threatening condition with an average time from diagnosis to death of only 30 months without effective and appropriate treatment. BHF-funded research has:

- Led to replacing higher risk invasive diagnostic cardiac catheterization in young patients with PH.
- Supported the development of novel therapies that have increased the survival and quality of life of people with PAH and CTEPH.



Without treatment, around only 3 out of 10 people with severe PH survive five years after diagnosis.

Thanks to novel therapies, five-year survival after diagnosis has increased to around 5 in 10 for people with CTEPH and 7 in 10 for people with PAH.

Changing the lives of people living with pulmonary hypertension

In 2017, the Pulmonary Hypertension Association UK ran a survey among PH patients to find out what it means to live with PH.*

87% of people with PH said their PH treatment and management had improved their overall quality of life (45% said it had improved it 'a lot').

"I am able to do a lot more than I could before treatment, but now I know my limitations. I'm alive to see my beautiful grandchildren, which before diagnosis I didn't think I would be.

PH patient surveyed by PHA UK

"(When my treatment started) I no longer needed my mobility scooter, came off the transplant list, and went back to the job I trained for.

PH patient surveyed by PHA UK

*PHA UK 2017 survey results

Building NHS capacity

In 2002, BHF Professor Glennis Haworth founded the UK Pulmonary Hypertension Service for Children, which she led for many years. This clinical network, the first of its kind in the world, helped to identify the best treatments for children with pulmonary hypertension, and still cares for children throughout the UK with the condition. Professor Haworth's work has been instrumental in improving the survival rates of these children.

Pulmonary hypertension specialist centres in the UK

- Golden Jubilee Hospital, Glasgow
- The Freeman Hospital, Newcastle
- The Royal Hallamshire Hospital, Sheffield
- Royal Papworth Hospital, Cambridge
- The Royal Free Hospital, London
- The Royal Brompton Hospital, London
- Hammersmith Hospital, London
- Great Ormond Street Hospital, London

Research into pulmonary hypertension in the UK is well embedded in this network of hospitals, which allows clinicians and researchers to establish cohorts of patients and create large biobanks, key to finding new ways to treat pulmonary hypertension.

Impact of the BHF seen by international experts

"This report highlights the leadership and foresight of the British Heart Foundation in funding major breakthroughs of historical significance that have been essential to our current understanding of pulmonary hypertension and to the development of treatments used around the world, and that pave the way for finding a cure for this devastating condition.

Professor Marlene Rabinovitch, Stanford University

"The BHF contributes a large amount to improving understanding of pulmonary hypertension and outcomes for patients. PH is a rare disease, so its visibility on the BHF website is appreciated. And affecting both the lungs and heart means PH sits in a 'no man's land' between cardiology and respiratory, so the work the BHF is doing is really important in encouraging understanding and raising awareness of the condition.

Dr Iain Armstrong, Chair of the Pulmonary Hypertension Association UK

Looking to the future

BHF-funded research has helped to improve the lives of many people with PH. However, we still have no cure and an imperfect understanding of the causes of this condition.

More research is needed, and the world-leading expertise in PH research in the UK still needs the BHF's support. We confidently expect that new ground-breaking science and technical advances, building on previous BHF-funded research, will lead to further successes in combatting PH.

For references, supplementary information and more on the impact of BHF-funded research into pulmonary hypertension please visit **bhf.org.uk/impactofPH**

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bhf.org.uk