

### The future may be on hold, but it has not been cancelled



BHI Director Gianni Angelini reflects on a turbulent year.

The COVID-19 pandemic made 2020 a year like no other. It caused major disruption to our cardiovascular research and teaching, which is continuing into this year. Clinical translation research has virtually stopped, and basic science work has been significantly curtailed by the limited access to laboratories.

Charities, which are the backbone funders of our work, are experiencing unprecedented difficulties and this translates to reduced grant awards. However, the renewal award of our BHF-funded PhD programme in Integrative Cardiovascular Science is excellent news – see the next page to find out more. And, at the same time, the use of virtual platforms has transformed our work and opened avenues which were unthinkable a year ago.

So, despite the gloom and doom, the pandemic is giving us a unique opportunity to regroup and reflect on what we did in the past, and what we can do better in the future.

These are the things that have not changed:

- Our determination to continue to stand out as the leading academic cardiovascular centre in the UK, and amongst the foremost worldwide.
- Our ability to turn innovations into benefit for adult and paediatric patients, and the health system.
- Our creation of an environment where clinicians, basic scientists and clinical research methodologists can thrive, attract the most talented individuals and produce world-leading research.

- Our resolve to facilitate a smooth and timely transition to the next generation of cardiovascular clinicians and researchers.

This last point is possibly the most relevant for somebody heading towards the twilight of his career! We have an obligation to nurture and mentor our future research leaders by encouraging them to build the confidence to lead. We must pay more attention to our early- and mid-career researchers and encourage them to play a major role at the heart of our activities. They are the next generation who will guarantee our continued success.

The future is still there for you to grab: it has not been cancelled.

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# BHF PhD funding renewed

Alastair Poole explains the impact this will have on our Integrative Cardiovascular Science PhD programme.



In December 2020 the British Heart Foundation (BHF) announced new funding for its flagship four-year PhD programmes at 12 universities, aimed at nurturing the next generation of cardiovascular research leaders.

At the University of Bristol, we have been running the popular PhD programme in Integrative Cardiovascular Science since 2017, with tuition fees and research costs fully-funded by the BHF.

Understanding the biology and medicine of the cardiovascular system now requires approaches that cross-bridge disciplines, with our current cohort of students working across fundamental bioscience, clinical science and population health.

In this renewal, we aim to build on this successful strategy, introducing new disciplinary strands, supervisors and training in digital health, data analytics, coding and bioengineering. This aligns to the BHF strategy in aiming to prevent disease, identify and manage risk factors, through large scale genomics, data science, AI and multiparameter monitoring of environmental and

medical measurements using novel personal and environmental devices. Bioengineering is now seen as an important component of regenerative medicine, and capitalizing on our broad base of expertise in Bristol, we have incorporated several new supervisors into this element. The renewed programme, which is recruiting now, includes two exciting new disciplines in bioengineering and digital health. These will provide additional depth and breadth to the training for our students and further opportunities for innovative cardiovascular discovery.

When the funding was announced, Professor Metin Avkiran, the BHF's Associate Medical Director, said:

"Today's PhD students are tomorrow's leaders in cardiovascular research. At this difficult time, it is more important than ever to maintain that pipeline of scientific talent and discovery towards future advances in the prevention, detection and treatment of heart and circulatory diseases."

We look forward to welcoming our newest BHF PhD students in 2021.

PhD student Ffion Jones talks about what she enjoys about the programme.

[Watch on YouTube:](#)



# Mechanisms of cardiovascular complications in COVID-19



Paolo Madeddu discusses the progress of a timely research project.

## Q: Why is this research significant?

The coronavirus that causes COVID-19 enters the body through the epithelial-endothelial barrier of the lung and then spreads systemically. Its most severe manifestation is severe acute respiratory syndrome, where the epithelial-endothelial barrier is damaged to a level that fluid escapes into the alveoli. This makes it difficult for the lung to expand and allow the physiological exchanges of gases, resulting in severe hypoxia, shock and systemic organ damage. Organ damage is also caused by the virus' ability to bring about a systemic inflammatory response and evade the immune system's defences.

Pericytes - cells surrounding the vasculature - are essential to maintain vascular stability. We think that they can be damaged by the virus, which contributes to pulmonary and systemic damage. We also think that the damage starts very early, when the viral S protein engages with the entry receptors expressed on cells. This is sufficient to activate detrimental signals in the pericytes and eventually prepare the ground for the virus to spread.

## Q: What do you aim to do?

Our research aims to determine which receptors are expressed by human cardiac pericytes (ACE2 and also CD147, which is a more controversial receptor); determine if the S protein alone can induce signalling in exposed pericytes in culture; understand the functional consequences; and verify whether we can shield pericytes by blocking the interaction between S protein and receptors.

## Q: How are you progressing?

The data we have gathered confirm the entry receptor CD147 is expressed in pericytes. However, the expression of ACE2 receptors was low.

The S protein induces the phosphorylation of ERK1/2. This is a kinase enzyme involved in various cellular functions, but also used by the virus to activate RNA polymerase (the enzyme that makes copies of RNA and is used by the virus to make copies of itself). This reaction makes the pericytes less able to support the vascular network and also induces them to secrete inflammatory molecules typical of the cytokine storm. The instability is more evident in adult cells compared with young cells.

We can inhibit these reactions with an antibody directed to the CD147 receptor, which suggests this is a viable method to shield human pericytes.

Read the pre-print article in [BioRxiv](#) and [the Lancet](#). Both are accessible to everyone to read and have received a lot of attention to date.

## Q: What's next?

Because cardiovascular patients are more susceptible to complications from COVID-19, we want to integrate the shielding approach of vascular cells within a more general strategy to protect the human body at the early stages of the disease.

A BHF grant is funding our work for one year. This work is carried out by Dr Elisa Avolio on cardiac pericytes provided by Professor Massimo Caputo, both acting as co-PIs.

As part of Bristol's collective research effort into COVID-19, we are seeking an additional contribution from other charities and funding agencies to work with fellow Bristol researchers to generate an aerosol containing blockers of entrance and attachment receptors.

# Preventing vascular damage associated with protein in urine



Becky Foster and Simon Satchell received a three-year BHF grant to investigate endothelial glycocalyx restoration. Principal Investigator Becky explains:

Proteinuria (protein within the urine) is an independent risk factor for cardiovascular disease. This is not only relevant for patients with kidney disease, but also for five per cent of the general population who have low-level proteinuria. A two-fold increase in proteinuria increases risk of cardiovascular mortality by 30 per cent.

If we knew how proteinuria is linked to vascular damage, we would potentially be able to treat these patients to prevent vascular disease.

Proteinuria begins in the filtering microvessels that form the glomerulus in the kidney. The microvessel wall is a specialised filtration barrier made up of endothelial cells, a glomerular basement membrane and epithelial cells (podocytes). Podocyte damage is often key to major glomerular protein leakage. A proteoglycan-rich endothelial glycocalyx (eGlx) layer lines all blood vessels. Damage to eGlx leads to increased vascular leakage around the body, which can progress to vascular disease.

We have also shown that, in conditions of proteinuria, eGlx is also damaged in non-kidney blood vessels, and that this is associated with increased vascular leak. Heparanase is an enzyme

that is upregulated in conditions of proteinuria by podocytes and also induces eGlx damage.

Our study will address our novel research question, that podocyte-induced heparanase expression causes vascular eGlx damage in proteinuric disease.

From this project, we will know whether heparanase upregulation by podocytes induces vascular damage, whether podocyte damage in proteinuria causes eGlx vascular damage and whether this is dependent upon heparanase. We will also use a clinically relevant heparanase inhibitor, which can be used to drive translation into the clinic for these patients.

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# Restoring respiratory sinus arrhythmia in heart failure



**A CiC award will enable Eva Sammut to test the safety and feasibility of a novel device to reinstate RSA in dyssynchronous heart failure.**

Confidence in Concept (CiC) awards fund proof of concept studies, which provide robust evidence of the feasibility of a proposed solution to a clinical need.

Eva Sammut, NIHR-funded academic clinical lecturer in Cardiology at the BHI received a £100K Elizabeth Blackwell Institute MRC CiC award in January to look at the feasibility, safety and effectiveness of a novel device to restore respiratory sinus arrhythmia in patients with heart failure.

## **Q: Why is your research significant?**

Heart failure is a global clinical pandemic with clear unmet clinical need. Despite some advancements in therapy, prognosis remains poor with a 50 per cent five-year mortality representing a significant societal and healthcare burden.

Respiratory sinus arrhythmia (RSA) is a physiological phenomenon of a subtle increase of heart rate during inspiration and the converse during expiration. RSA is a major component of physiological heart rate variability, a sign of good cardiac health, and is known to be lost in patients with heart failure. Loss of RSA is associated with increased ventricular arrhythmia and sudden cardiac death. Restoring RSA in heart failure patients could improve their life expectancy and markedly reduce hospitalisation costs. Existing preclinical models are inadequate to validate the safety of new treatments in this priority area.

## **Q: What are you developing?**

Our group have developed a novel device which is able to reinstate RSA. Our preliminary results are very promising and demonstrate feasibility. Further proof of concept data from an advanced preclinical model is now pivotal to ensure the safety, feasibility and applicability of the new device to progress it toward bedside to benefit patients.

This project will test the safety and feasibility of this new technology in the setting of dyssynchronous HF. This is a complex form of heart failure that responds poorly to the best available current treatment – a specialised pacemaker named cardiac resynchronisation therapy. This study will be performed at the University's Translational Biomedical Research Centre facility. We will develop an advanced preclinical model of dyssynchronous heart failure with balloon catheter myocardial infarction and superimposed pacemaker-induced ventricular dyssynchrony. Next, we will use this model to test this novel pacemaker approach to reinstating respiratory sinus arrhythmia in addition to cardiac resynchronisation therapy.

## **Q: Who are you working with?**

A unique multidisciplinary team has been assembled including Professors Julian Paton, Raimondo Ascione and Alain Nogaret, and Drs Tom Johnson, Ed Duncan and Vito Domenico Bruno, who are co-applicants supporting this project.

We are also working in collaboration with Ceryx Medical, a spin out company formed by the universities of Bristol, Bath and Auckland.

## **Q: What next?**

We are delighted to receive this funding to be able to take this exciting new technology to the next developmental stage. This project is critical to ensure safety, feasibility and applicability of the new device in this setting. If positive results are demonstrated this would pave the way for larger, efficacy translational studies, with a view to reach patients in the NHS within the next five to six years.

## MINOCA study recruitment wraps up

The innovative MINOCA study recently completed its recruitment phase at UHBW.

One in 10 patients who suffer a suspected heart attack do not have a blocked or narrowed heart artery. These patients are classified as having a myocardial infarction with non-obstructive coronary arteries (MINOCA). Previously thought to be low risk, MINOCA patients were often discharged with no treatment or follow up. However, research shows that these patients have mortality of nearly five per cent at only 12 months.

MINOCA patients are more likely to have had a stressful event prior to admission and a history of anxiety or depression. Previous research has even suggested that people with a stress cardiomyopathy – a common cause of MINOCA – have structural and functional differences in their brain, which may lead to differences in emotional processing and increased sympathetic drive compared to people who do not develop this condition in response to stress.

The MINOCA study is investigating for the first time this link between the heart and the brain in MINOCA

patients. Over the last two years, the team - led by Chief Investigator Chiara Bucciarelli-Ducci - has conducted a functional brain MRI and a cardiac MRI, as well as blood tests, ECGs and questionnaires, on 100 participants within two weeks of being admitted to hospital, with follow up MRI scans at six weeks and six months.

Principal Investigator Matt Williams said:

“Our novel prospective study is looking to see if patients with MINOCA have specific functional and anatomical changes in their brain which might explain why they develop this condition. Ultimately, it may be possible to target increased stress related brain activity to reduce the risk of this condition and improve patient outcomes.”

The study has been funded by grants from Above and Beyond, the James Tudor Foundation and the Rosetrees Trust.

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# First use of ROB2 in Cochrane Review of Exercise Interventions for CHD

The Cochrane Review gathered evidence for the effectiveness of physical activity interventions for people with congenital heart disease.

Graham Stuart and Guido Pieles collaborated with Craig Williams at the University of Exeter to publish a Cochrane Review in October 2020.

It compared three types of interventions from 15 trials, including programmes designed to increase physical activity, aerobic fitness and health-related quality of life. It found some evidence for increased physical fitness and physical activity, although there are no data yet to suggest this results in fewer hospital visits.

Graham Stuart, Honorary Associate Professor in Sports and Exercise Cardiology, said:

“Exercise used to be discouraged in patients with CHD. This was poor advice and led to an increase in cardiovascular and psychosocial morbidity.

“Our Cochrane Review has shown that there is a need for further research to demonstrate why exercise benefits disordered cardiovascular physiology and to establish whether the multiple theoretical benefits of exercise training can translate into improved clinical outcomes.”

All authors of Cochrane systematic reviews are now expected to use the Cochrane Risk of Bias tool (ROB2) to assess the risk of bias in any randomized controlled trials they identify, to help people understand the trustworthiness of the findings. This was the first Cochrane Review to use ROB2 methodology.



[Read the review in the Cochrane Library.](#)

The review findings were also published in the “[Cochrane Corner](#)” of Heart.

[See the Cochrane editorial on ROB2](#)

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## Fundraisers go Above & Beyond

Two fundraisers with links to the BHI have been raising money for UHBW hospitals charity Above & Beyond during lockdown.

### Paul's story

Paul Hobbs has been a fundraiser for over 25 years, raising around £750,000 for 20 charities, hospitals, and organisations. Last year, he chose to support his local hospitals charity Above & Beyond.

Paul hoped to celebrate 25 years of fundraising with an event at Ashton Gate in September 2019, but this had to be postponed while he had life-saving heart surgery at the Bristol's Royal Infirmary's Heart Institute (BHI). The surgery was very successful, and Paul has since made a full recovery.

The event was rearranged for March 2020, but postponed again due to COVID-19, so Paul decided to hold an online auction instead. The auction raised £2,500, which will go to the BHI.

Paul said: "Staff at the BHI saved my life. Every staff member was fantastic in the way they cared for me. It's no wonder the unit has such a superb reputation across the UK.

"I'm making a great recovery from my operation. My fundraising auction was an opportunity to say thanks to the BHI staff that looked after me."

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*Staff at the BHI saved my life.”*



### Alex's story

A nurse who works at the BHI is selling soaps to raise money for Above & Beyond.

Alexandra Jenkins has worked at the hospital for two years and has seen the hospital benefit from funding from the NHS charity. She was working in the cardiac intensive care unit (CICU) on Christmas Day and her patients had presents to open, thanks to donations to Above & Beyond.

She said: "I started making soaps as a lockdown boredom activity and I had some interest from friends and family asking to buy them. I didn't really want to make a business out of it or make a profit, therefore I was inspired to raise money for Above & Beyond."

As well as working in the NHS, Alex has a personal connection to the BHI. Her husband Carl has had multiple cardiac operations and procedures, first at Bristol Royal Hospital for Children and later in the BHI.

Alex said: "The care he received at the BHI was part of the reason I chose to apply for a job there many years later."



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# The Bristol Heart Institute Steering Group

## Director

**Gianni Angelini:** BHF Professor of Cardiac Surgery and Cardiovascular theme lead at the NIHR Bristol Biomedical Research Centre

## Deputy Director

**Alastair Poole:** Professor of Pharmacology and Cell Biology

## Members

**Dr Giovanni Biglino:** Biostatistics

**Dr Chiara Bucciarelli-Ducci:** Imaging

**Joseph Butler:** Research Development Associate, Faculty of Health Sciences

**Professor Massimo Caputo:** Congenital heart surgery

**Dr Becky Foster:** Renal, diabetic and hypertensive disease

**Professor Sarah George:** Cardiovascular signalling

**Dr Emma Hart:** Cardionomics

**Dr Andrew James:** Cardiac biology

**Dr Jason Johnson:** Pathology of cardiovascular diseases

**Professor Paolo Madeddu:** Cardiovascular regenerative medicine

**Professor Stuart Mundell:** Vascular biology and atherothrombosis

**Professor Ruth Newbury-Ecob:** Clinical genetics

**Dr Angus Nightingale:** Consultant cardiologist

**Dr Guido Pieleles:** Sports and exercise cardiology

**Dr Simon Satchell:** Renal, diabetic and hypertensive disease

**Professor Saadeh Suleiman:** Cardiac biology

**Professor Nic Timpson:** Population health and epidemiology

Thank you to everyone who has contributed to this edition.

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