FOUNDATION FOR CIRCULATORY HEALTH

Funding the fight against cardiovascular disease globally

Preventing cardiovascular disease by research innovation

Cardiovascular disease is the leading cause of death worldwide. In the United Kingdom, the prevalence of heart disease and stroke is among the highest in the world, being responsible for almost 200,000 deaths each year. Tragically, over the next 20 years, worldwide these numbers are projected to increase dramatically. However, this is not inevitable – it need not happen – given that the associated risk factors are largely identified.

The Foundation for Circulatory Health was set up to facilitate and promote the International Centre for Circulatory Health (ICCH), a collaborative team of internationally renowned scientists and clinicians in cardiovascular medicine. ICCH aims to deliver an integrated research strategy in circulatory medicine and apply results of this research to advance standards of care in the prevention and treatment of cardiovascular diseases in a multi-ethnic society. The scope of this research includes:

- Clinical trials; the ICCH Trials Unit is an international leader in large-scale clinical trials
- Patient-based research in cardiovascular disease and diabetes
- Vascular studies to improve understanding of disease mechanisms
- Cardiovascular disease epidemiology with emphasis on different ethnic groups

The Foundation also supports the Young Researcher Programme at ICCH. Under this programme, a team of dedicated young researchers work on a range of innovative projects under the supervision of ICCH members. These projects focus on practical and realistic ways by which circulatory disease can be prevented and how these ways can be applied to improve clinical practice. Their work also involves the interpretation of the vast amount of data collected from major trials, some of which were undertaken by the ICCH Trials Unit. The scale of the success achieved by the young researchers is reflected in the number of awards and prizes they have received. This update is a selection of some of the ongoing research activities at ICCH.

We believe that the ICCH Young Researcher Programme means that the Centre continues to be a unique and powerful force to reduce the anticipated global impact of cardiovascular disease and to improve patient care. But it is only with your help and support that the Foundation can provide essential funding to maintain the ongoing success of this research programme.

Jeremy Skinner
Chairman of the Board of Trustees
The Foundation for Circulatory Health

The International Centre for Circulatory Health (ICCH)

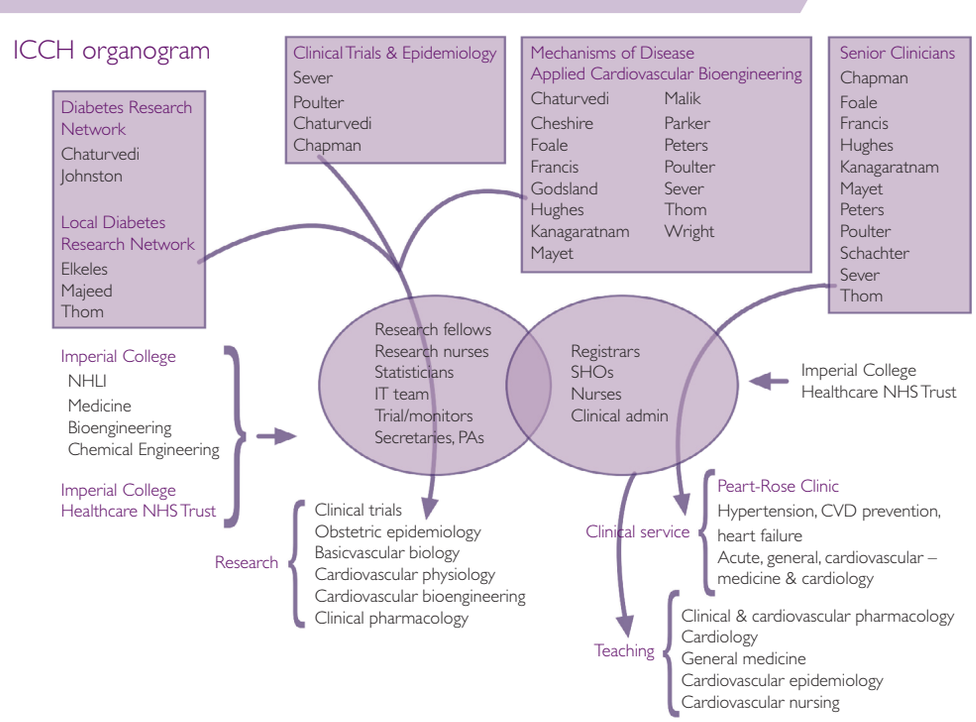
Mission statement

The mission of ICCH is to create and maintain a centre of excellence with an integrated research strategy in the field of circulatory medicine, as well as apply findings from research to advance standards of care in the prevention and treatment of cardiovascular and metabolic disease.

Our vision includes:

- Delivery of a strategic, multidisciplinary research programme
- Development and implementation of improved models of care
- Provision of a first class clinical service for cardiovascular disease prevention and treatment
- Communication of research results to healthcare professionals and the wider public
- Creation of an environment that develops individual careers in clinical and basic research.

One of the hallmarks of ICCH is effective cross-disciplinary collaboration between clinical and research staff, enabling them to contribute to a wide variety of projects in different fields. Successful integration across units at ICCH is the key to driving excellence in clinical services, research and teaching.



The ASCOT database: a valuable research resource

The Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) was one of the earliest trials in the UK and Europe to show the benefits of cholesterol lowering with statins. ASCOT also demonstrated that newer drug combinations were superior to earlier treatments when lowering blood pressure. Analyses of the ASCOT database have led to several important publications with implications for clinical management and future research. This database is held at ICCH.

Dr Ajay Gupta has looked at which factors predicted the likelihood of developing diabetes in hypertensive patients. This research showed that patients treated with the combination of two newer blood pressure lowering drugs (the calcium channel blocking drug, amlodipine and perindopril, an angiotensin-converting enzyme inhibitor) resulted in about one-third lower risk of developing diabetes compared with those treated with older drug combinations (beta-blocker and diuretic). In addition, baseline fasting plasma glucose, body mass index, serum triglycerides (fats within the blood) and systolic blood pressure were associated with increased risk for diabetes.

Conversely, high baseline levels of high-density lipoprotein cholesterol ('good cholesterol'), alcohol intake and age >55 years were protective. Increased levels of fasting plasma glucose and the development of diabetes increased the risk of cardiovascular outcomes. On this basis, Dr Gupta suggests that the adverse effects of the beta-blocker plus diuretic combination used in ASCOT (atenolol plus thiazide) may be responsible.

'In the US alone, it is estimated that about a quarter of a million cases of diabetes could be prevented each year by judicious use of antihypertensive agents. Our data indicate that the appropriate choice of antihypertensive combination therapy can reduce the risk of developing diabetes and experiencing cardiovascular events such as heart attack.'

Dr Ajay Gupta

In a second project, **Dr Gupta** and **Dr Stylianos Mastorantonakis**, used the ASCOT database to show that the metabolic syndrome (a clustering of risk factors for cardiovascular disease, including hypertension, dyslipidemia and impaired glucose metabolism), was associated with increased risk of diabetes, stroke and death, beyond that associated with its individual components. Since, in ASCOT, cancer was a major cause of death (after cardiovascular causes), they plan to investigate whether the metabolic syndrome is also an independent predictor for cancer morbidity and mortality, and if so, whether insulin resistance represents a possible link.

'We plan a systematic meta-analysis, the first of its kind, to establish whether there is a link between metabolic syndrome, insulin resistance and risk of cancer morbidity and mortality.'

Dr Ajay Gupta and Dr Stylianos Mastorantonakis

Ethnicity and cardiovascular disease

Therese Tillin is a clinical epidemiologist currently working on a portfolio of studies exploring the risks of vascular and metabolic diseases among ethnic groups. One of these studies is the SABRE study, a 5-year programme grant funded jointly by the Wellcome Trust and British Heart Foundation, which is following more than 4,000 people of European, South Asian and African Caribbean descent for a 20-year period. Over 2,000 survivors from this study will undergo detailed non-invasive clinical investigations.

Her other research work includes the use of intravascular ultrasound to characterise atherosclerotic plaque and the response of the coronary arteries to the presence of plaque in people of South Asian and European descent. She is also planning a programme of work to determine the effects of different sites of fat distribution on insulin resistance and heart disease in both young and older people.

'The SABRE study aims to identify explanations for the striking differences in diabetes and cardiovascular disease between ethnic groups.'

Therese Tillin

Optimising hypertension treatment in different ethnic groups

Most guidelines for managing hypertension do not consider the ethnicity of the patient in the selection of initial or subsequent treatment. To address this, **Dr Ajay Gupta** investigated differences in the blood pressure response between 5,425 white, black and South Asian patients with hypertension included in ASCOT. Patients received a beta-blocker or calcium channel blocker as monotherapy and a diuretic or angiotensin- converting enzyme inhibitor as second-line therapy.

This study has provided the first evidence of ethnic differences in the blood pressure response to second-line agents. These findings question current recommendations from the British Hypertension Society and NICE on the choice of second-line agents for black hypertensive patients. To address this question, a trial is planned to compare the blood pressure lowering efficacy of a two-drug combination recommended by these guidelines with the proposed combination of calcium channel blocker and diuretic, individually shown to be effective in black hypertensive patients.

'If this combination is shown to be more effective in lowering blood pressure, this would potentially lead to a change in national guidance for black patients with hypertension. This would have the potential to improve blood pressure control and reduce adverse cardiovascular outcomes among the high-risk patients belonging to this ethnic group.'

Dr Ajay Gupta

Patient-based research

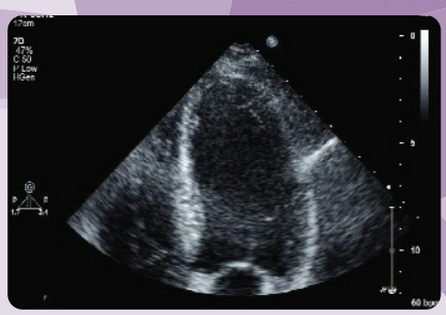
Assessing right ventricular function after cardiothoracic surgery

Coronary artery bypass has come a long way since the 1960s, when this life-saving procedure was first performed. St Mary's Hospital was one of the first centres in the UK to launch the da Vinci® robotic minimal invasive cardiothoracic surgery programme, which permits surgeons to perform 'key hole' coronary bypass and valve repair by operating three robotic arms using joysticks and a console.

With the support of the British Heart Foundation, **Beth Unsworth**, senior cardiac physiologist, is working alongside cardiothoracic surgeons to research the effects of cardiothoracic surgery on right ventricular function using echocardiography imaging techniques (a non-invasive ultrasound scan of the heart).

'We are assessing the immediate benefits that this novel, minimally invasive approach provides in the preservation of right ventricular function compared to traditional surgical techniques. We are also interested in the role that the pericardium plays in the preservation of right-sided heart function.'

Beth Unsworth



Imaging in heart failure patients

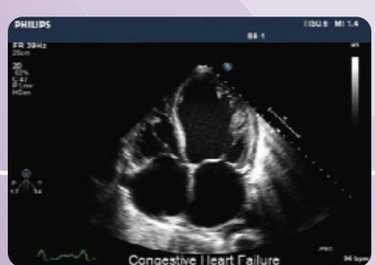
Assessing and optimising pacemaker settings within the heart failure population

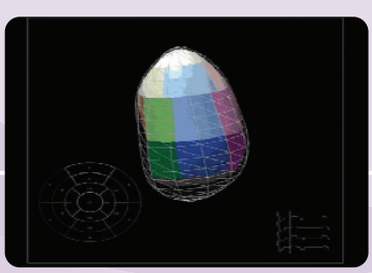
Dr Punam Pabari is a Cardiology Registrar supported by the British heart Foundation carrying out a PhD in patients with heart failure and biventricular pacemakers.

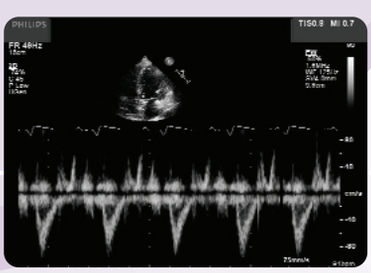
Her research identifies the beneficial impact of different pacemaker settings on blood pressure and heart function. These studies use ultrasound (advanced echocardiography) to measure response and provide images for analysis. These images and the accompanying measurements are acquired at rest and following exercise allowing optimal pacemaker settings to be identified. For the patient the aim will be to increase the ability to exercise and to improve overall physiology.

'This will allow us to understand the physiology behind the disease and changes during treatment, maximise the response from CRT devices and provide information for future patients who may benefit from them.'

Dr Punam Pabari



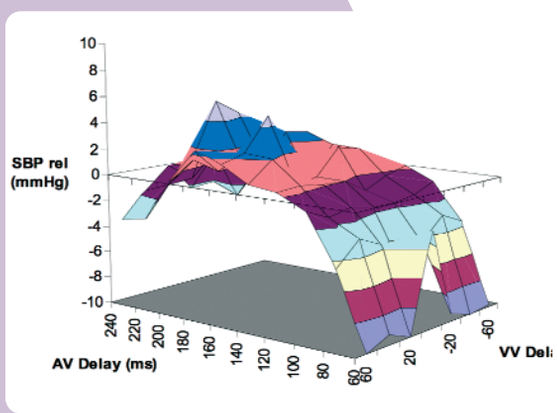




Optimising pacemaker settings

Surprisingly, dramatic developments in heart failure pacemakers have not been accompanied by development of optimal ways to tune them in to the ideal settings to benefit the patient.

In award-winning research as part of his PhD at ICCH, **Dr Zachary Whinnett** created a new, quick, cost-effective and highly consistent way to tune new pacemakers to the ideal settings.



'Mr Wilkins, a patient in a nearby hospital, was terribly disappointed when he had his heart pacemaker fitted to treat his heart failure. Instead of the prompt and dramatic benefit he had been hoping for, there was no improvement in his symptoms. It turned out that the pacemaker had been left at standard settings (like a radio left at factory settings, and not tuned in to a preferred station). Mr Wilkins was referred to us because we had developed a new method for fine-tuning pacemaker settings to get the maximum benefit for the patient and we were able to help him.

ICCH is now working to have this innovative development made available to all patients with pacemakers throughout the world, to ensure that they obtain the full benefit of the procedure that they undergo.'

Dr Zachary Whinnett

Dr Andreas Kyriacou has been awarded a Clinical Research Training Fellowship by the British Heart Foundation for research at ICCH. Part of this involves following on from Dr Whinnett's success, to develop a similarly reliable and inexpensive method that will consistently fine-tune patients' pacemakers.

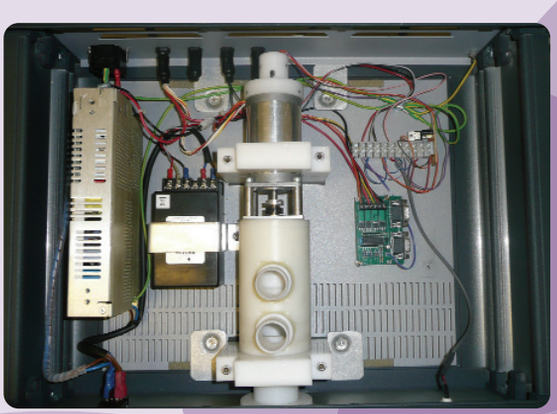
New technology for treating central sleep apnoea

Central sleep apnoea is an abnormal pattern of breathing commonly seen in heart failure patients. Breathing is characterised by periods of hyperventilation followed by periods of hypoventilation or even a pause in breathing. Sometimes the patient is unaware that they are doing this, although it can be obvious to those around them. Patients are also tired during the day and have abnormal blood pressure patterns.

A collaborative team of researchers at ICCH, including **Dr Charlotte Manisty, Dr Resham Baruah** and **Keith Willson,** Principal Research Fellow, is using pioneering technologies to treat sleep-disordered breathing in heart failure patients.

Intelligent Breathing

The Intelligent Breathing Project aims to treat sleep apnoea by the delivery of carefully-timed doses of carbon dioxide, administered only during pathological breathing episodes



Internal view of the prototype Carbon Dioxide Administration System developed for the Intelligent Breathing Project.

according to a novel mathematical model. This improves the stability of patients' breathing without having to apply the conventional, uncomfortable tight-fitting pressurised face mask used in continuous positive-pressure therapy.

This new method of stabilisation has won awards from the Royal Society of Medicine and the Medical Futures Technology organisation of the Department of Health.

'We hope that continued development may allow us to ease the physical, mental and psychological burden of sleep disturbance in patients with sleep apnoea.'

Dr Charlotte Manisty

PACEMAX

Another project involves the use of cardiac pacemaker technology to try to stabilise ventilation. ICCH has been involved in a decade-long programme of research using biomathematical approaches to the complex interplay of cardiovascular, respiratory and metabolic physiology in cardiovascular disease. One of the insights involved the use of mathematics to predict a (previously undescribed) method of dynamically manipulating ventilation using a standard cardiac pacemaker.

'PACEMAX allows us to quantify the haemodynamic response to pacemaker settings by simple non-invasive measurement such as blood pressure.'

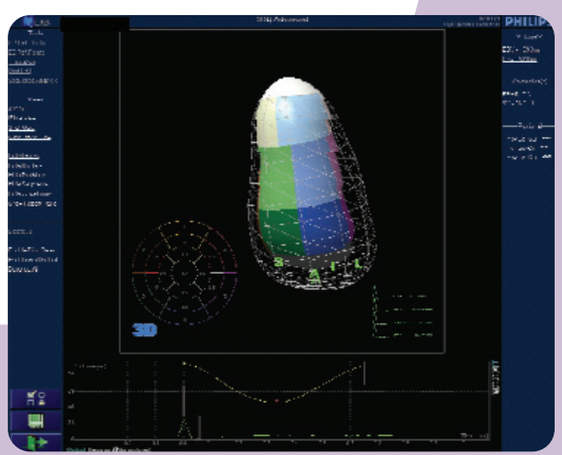
Keith Willson, Principal Research Fellow at ICCH

'We hope that in the future this technology could be included on all cardiac pacemakers used in heart failure.'

Dr Resham Baruah

New technology to assess leaking heart valves

When a heart valve leaks, cardiologists are forced to use very simple 'eyeball' methods to assess whether the leak is mild, moderate or severe. **Dr Corinna Bergamini,** an international research fellow from the University of Verona's well-known cardiac imaging service, is collaborating with Imperial College's valve disease team to develop a new technology for measuring the severity of leaking heart valves. Dr Bergamini is working with Dr Anura Malaweera, Imperial College Medical School, and Professor Kim Parker and Professor Yun Xu, Imperial College Engineering Department to develop a new method which could permit rapid, reliable quantifications of the size of the leak on heart scans.



'Innovative technology will make it easier to follow patients' progress, decide who should have surgery and when, and to trial new therapies more effectively.'

Dr Corinna Bergamini

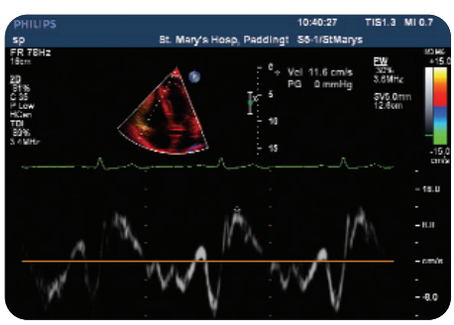
Scoring diastolic heart function

Heart failure can be of two types: a failure of the heart to pump properly (systolic failure) or relax properly (diastolic failure). While the former can be accurately and reliably diagnosed, diagnosing diastolic heart disease can be challenging.

With the help of the recently instituted Academic Foundation Programme, **Dr Hemang Yadav,** a senior house officer working within Imperial College NHS Trust, is involved in research at ICCH aimed at improving clinical imaging in heart failure. Using tissue Doppler imaging, a type of echocardiography, Dr Yadav has developed an age-standardised scoring system for more reliably classifying diastolic function.

'This score might help us to diagnose (and thus treat) diastolic heart dysfunction sooner than we are able to do currently, hopefully improving the outcome of patients with this often disabling condition.'

Dr Hemang Yadav



Vascular research

Retinal imaging and cardiovascular health

The eye offers a unique window through which blood vessels in the retina (the layer of light sensitive cells at the back of the eye) can be observed without complex or risky intervention. Physicians routinely examine the eyes of their patients using a hand-held ophthalmoscope to check for abnormalities that might indicate the presence of high blood pressure or diabetes. Research by Professor Simon Thom and his team at ICCH has shown that computer analysis of photographs of the retina can provide additional information on cardiovascular health, possibly in advance of other clinical indications. This has practical advantages as retinal photographs can be obtained easily in just a few minutes using a special camera, widely available in clinics throughout the world.

In collaboration with the University of Wisconsin and using an image analysis technique developed by **Nick Witt,** the team showed that abnormalities in the geometry of retinal vessels, such as the relationship between their diameters where the vessels divide, can predict the subsequent development of heart disease, independently of other risk factors. The geometry of the retinal vessels is regulated by the endothelium, a thin layer of cells lining the vessels. Dysfunction of this layer is believed to give rise to the altered geometry, and also to increase the risk of atherosclerotic lesions that may lead to heart disease and stroke.

'By identifying such risks in advance, treatment may be given at an earlier stage, improving the outlook for the patient.'

Nick Witt

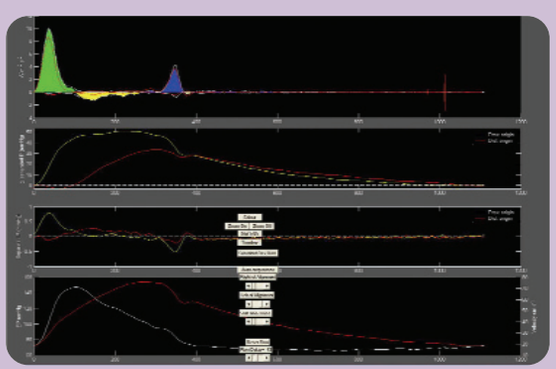
The retina has a higher oxygen requirement than any other organ in the body, and this makes it exquisitely sensitive to diseases which impair its blood supply. This blood supply is delivered by a network of blood vessels – a tree of small arteries – that lies flat on the retinal surface. We know that the shape of this tree becomes deranged at early stages in the development of hypertension and diabetes. It is likely that even minor derangements in successive branches of the tree will have a big impact on blood supply when multiplied across the whole network. **Dan Liu** is building mathematical models that capture the geometric features of the eye in normal and diseased state. This approach will help us to determine the impact of hypertension and diabetes on the efficiency of retinal blood flow and to identify which abnormalities are most influential. In turn this should offer new clues to early clinical detection.

'By applying this integrated model to patients with hypertension or diabetes, we hope to further our understanding of the relationships between retinal blood flow and cardiovascular disorders.'

Dan Liu

Wave Intensity Analysis

Researchers at ICCH have developed completely new methods of analysing the complex interactions between pressure and flow that occur within the coronary arteries during cardiac contraction and relaxation. Wave Intensity Analysis, pioneered at Imperial College by collaborative research between Professor Kim Parker and **Keith Willson** is one of these methods. This technique measures blood pressure and the speed of blood flow at the same time and in the same place using special sensor wires placed in the main blood vessel leading from the heart. This improves understanding of the generation of blood pressure and factors which influence it.



In his PhD research, **Dr John Baksi** is using Wave Intensity Analysis to improve our understanding of how age affects the generation of blood pressure.

As we age, not only does blood pressure rise, but it also becomes more 'pointy', with a bigger and sharper upstroke in pressure. This may contribute to the increased rate of heart disease and stroke in older people. Doctors used to believe that the reason for the increase in 'pointiness' of blood pressure was that pressure waves, travelling outward from the heart through the arteries, were more powerfully and quickly 'reflected' back towards the heart. As a result, treatments have been targeting this reflection process.

However, Dr Baksi has recognised that this picture might be false. In a series of experiments, he is testing the possibility that this change is nothing to do with reflections at all, but instead, is the result of changes in the pliability of the large arteries.

'The reason why these drugs are not as effective in preventing heart attack and stroke as we would like, might be that they are targeting the wrong problem. If proven, this will make a huge impact on the way we think about, and treat, high blood pressure, the greatest contributor to preventable cardiovascular death in the world.'

Dr John Baksi

Investigating blood flow in the coronary arteries

The movement of blood in the coronary arteries is still not fully understood. Unlike other organs, which receive a pulse of blood flow every time the heart contracts, the heart muscle itself compresses its own blood supply during its contraction. ICCH has developed a completely new method of analysing the complex interactions between pressure and flow that occur within the coronary arteries during cardiac contraction and relaxation.

Dr Justin Davies is using this method to identify a series of energy waves responsible for directing blood flow in the coronary arteries. These waves are detrimentally reduced in the abnormal thickening of the heart muscle caused by high blood pressure.

More recently, Dr Davies has developed a new technique to assess the importance of changes in the reservoir properties of the aorta in regulating blood pressure, and the impact of ageing and disease.

'This new reservoir technique has the potential to aid the understanding of the mechanisms of hypertension, and may be useful in assessing the modes of actions of different antihypertensive agents.'

Dr Justin Davies

Dr Nearchos Hadjiloizou, a British Heart Foundation Junior Research Fellow, is investigating the effect of left ventricular function on coronary haemodynamics. Normally, the blood supply to the heart comes from the left and right coronary arteries. While these arteries originate from the same level of the aorta and experience the same aortic pressure, their flow patterns are strikingly different. Dr Hadjiloizou accounted for this difference by investigating wave generation in each of these arteries.

'I am currently applying this technique to account for the unique flow patterns seen in pathological states such as aortic stenosis and coronary artery disease.'

Dr Nearchos Hadjiloizou

What makes a coronary plaque vulnerable to rupture?

A collaborative research team from Imperial College, St Mary's and the Brompton Hospital has developed novel modelling techniques that can be used to map local haemodynamic stresses in the circulation. Interest is now focused on the more challenging setting of the coronary arteries.

Dr Ryo Torii is using this state-of-the-art technology to develop a combined *in vivo* imaging and computational technique for use as a predictive diagnostic tool for identifying plaques (the build-up of hardened fatty material in the arteries) that are vulnerable to rupture.

'Identifying those patients at risk will allow us to use interventions (such as coronary artery stents) to prevent plaque rupture and heart attack.'

Dr Ryo Torii

How can we predict blood flow in artery stenosis?

As part of her PhD, **Felicia Tan** is developing and validating innovative models for predicting flow patterns and the resultant forces in moderate-to-severe stenoses (narrowing of the arteries). Because blood flow changes from laminar (flowing in straight layers) to turbulent (chaotic) in these situations, the available models may not be valid.

'Developing suitable and efficient turbulent flow models may allow us to accurately predict flow patterns in patients with moderate-to-severe stenoses.'

Felicia Tan

Translating ideas to studies

As Clinical Studies Co-ordinator within the Mechanisms of Disease Group, **Emma Coady** has a key role translating grant proposals into workable clinical studies. Her work involves a range of activities including preparing grant proposals, training staff in a variety of clinical study procedures, and ensuring data management/ quality control systems are in place. Emma is also involved in a number of clinical trials in hypertension, as well as studies investigating ethnic differences in cardiovascular disease and diabetes within ICCH, nationally and internationally.

'I co-ordinate two clinical trials on hypertension and diabetes within ICCH and two sub-studies within the ALSPAC cohort (Avon Longitudinal Study of Parents and Children) at the University of Bristol. I am also part of the SABRE study, involving a large tri-ethnic cohort undergoing detailed non-invasive procedures.'

Emma Coady

International and national awards

Innovative research from the Young Researcher Programme at ICCH has resulted in many national and international awards

Resham Baruah
- 2008 Winner, British Junior Cardiologists Association Young Investigator Award
- 2008 Commendation, Cardiovascular Innovation Awards [*Intelligent Breathing*]

Charlotte Manisty
- 2008 Winner, British Society of Echocardiography Annual Abstract Award
- 2008 Finalist, British Junior Cardiologists Association Young Investigator Award
- 2008 Highly Commended, Medical Futures Award
- 2007 Winner, National Heart Lung Institute Annual Abstract Award
- 2006 Winner, Royal Society of Medicine President's Medal for Cardiovascular Research
- 2006 Runner-up, British Hypertension Society Young Investigator Award

Beth Unsworth
- 2008 First prize, European Council for Cardiovascular Research, Experimental Medicine Section

John Baksi
- 2008 First Prize, Artery 8, Best Poster Presentation

Justin Davies
- 2008 Winner (overall clinical and basic science), British Hypertension Society Young Investigator Award
- 2007 Winner, Artery 8 Career Development Award
- 2006 Winner (clinical science), British Hypertension Society Young Investigator Award
- 2006 Winner, GlaxoSmithKline Royal Society of Medicine Fellowship Award
- 2006 Finalist, British Cardiac Society Research Workers Prize
- 2006 Runner-up, Royal Society of Medicine President's Medal
- 2006 Runner-up, UK Bioscience Research and R&D Parliamentary Award
- 2006 Finalist, British Junior Cardiologists Association Young Investigator Award

Nearchos Hadjiloizou
- 2008 Second Prize, Artery 8, Young Investigator Award
- 2007 Finalist, British Junior Cardiologists Association Young Investigator Award
- 2007 Winner, Artery 7, Young Investigator Award

Dan Liu
- 2008 Winner, German Society for Biomedical Technology student award for best presentation at the 4th European Congress for Medical and Biomedical Engineering, Antwerp, Belgium

Ryo Torii
- 2008 Runner-up, British Cardiovascular Society Young Research Workers' Prize for Basic Science

Zachary Whinnett
- 2008 Winner, Medical Futures Innovation Award
- 2008 Winner, Medical Futures Cardiovascular Award
- 2006 First prize, British Junior Cardiologists Association International Research Award

Keith Willson
- 2008 Winner, Medical Futures Innovation Awards [*Pacemax*]
- 2008 Commended, Medical Futures Innovation Awards [*Intelligent Breathing*]

Selected recent publications from the team

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