University of BRISTOL

re: search

Bristol Heart Institute issue

University of Bristol • June 2006

Mending a broken heart

The energy powerhouse

Plaques, cracks and heart attacks

Cardiovascular research in the 21st century

Cardiovascular disease accounts for almost half of all deaths in the UK, no less for women than men. Only through continued research will we understand why heart disease became such a huge problem for the beginning of the 20th century and how we might confine it to history in the 21st century.

The Bristol Heart Institute was established in 1995. Since then it has expanded substantially and it now brings together experts from many different departments across the University of Bristol and associated hospitals. Consequently, the Institute is now an internationally recognised centre of excellence for carrying out interdisciplinary cardiovascular research that can bridge the void between clinical and basic science. But we must always keep moving forward.

We are therefore working towards bringing people together from diverse disciplines into one central building that contains common core equipment and research facilities. We will also be seeking long-term funding to provide stability and continuity of people and resources.

The following articles have been chosen to illustrate some of the innovative research being undertaken at the Bristol Heart Institute. I hope you find them stimulating.

Professor Gianni Angelini
Chairman, Bristol Heart Institute

Letter from Sir Ranulph Fiennes

Patron of the Bristol Heart Institute

I first met Gianni Angelini, Professor of Cardiac Surgery at the University of Bristol, after I suffered a heart attack at Bristol airport. I was rushed to the Bristol Royal Infirmary where he operated on me. The double bypass I received was so successful that three months later I ran seven marathons on seven continents in seven days, to raise money for the British Heart Foundation. I was therefore delighted when I was asked to become patron of the Bristol Heart Institute in 2005.

I believe that for current treatments for all forms of cardiovascular disease to improve, and perhaps be prevented altogether, the underlying causes need to be better understood. Scientists and clinicians working together under the umbrella of the Bristol Heart Institute is an ideal way to achieve these aims.

I wish everyone in the Bristol Heart Institute the very best of luck in finding new treatments for heart disease in the years to come, as all of us will be the beneficiaries of their work. I cannot thank them enough.

contents

The Bristol Heart Institute	1
Bursting the bubble	2
Exercise and the heart	3
Predicting the risk of cardiovascular disease	3
Mending a broken heart	4
Keeping to the heart beat	6
The energy powerhouse	7
Plaques, cracks and heart attacks	8
Building a bypass to last	9

contacts

Dr Elinor Griffiths
Cardiovascular Facilitator
Department of Biochemistry
School of Medical Sciences
University Walk
Bristol BS8 1TD, UK
Email: Elinor.Griffiths@bristol.ac.uk

Details of Bristol Heart Institute members can be found at www.bristol.ac.uk/bhi

Bristol Heart Institute websites of individual departments
Biochemistry: www.bristol.ac.uk/biochemistry
Clinical Science South Bristol: www.bristol.ac.uk/clinicalsciencesouth
Community Based Medicine: www.bristol.ac.uk/fmd/communitybasedmedicine
Exercise & Health Sciences: www.bristol.ac.uk/ehs
School of Law: www.law.bristol.ac.uk
Pharmacology: www.bristol.ac.uk/pharmacology
Physiology: www.bristol.ac.uk/physiology
Social Medicine: www.epi.bristol.ac.uk

A PDF version of this publication is available at: www.bristol.ac.uk/bhi

Editor
Dr Cherry Lewis
Research Communications Manager
Cherry.Lewis@bristol.ac.uk
Tel: +44 (0)117 928 8086

Design & Print
CW Design
www.cw-design.co.uk

If you need part or all of this publication in an alternative format, please contact the editor.

Cover image:
Hybrid Medical Animation/Science Photo Library

The Bristol Heart Institute

Bringing together clinical and basic science to attack a huge problem

Cardiovascular disease is the UK's single biggest killer of both men and women. For every 100 people who die each year, 40 die from cardiovascular disease – that's 230,000 lost lives in the UK alone. Indeed, cardiovascular disease kills more people each year than all types of cancer combined. These are startling statistics.

The possibility of identifying genetic links for susceptibility to high cholesterol also provides an exciting new area of research.

High blood pressure is yet another factor that causes coronary heart disease and the risk of irregularities of the heart beat (arrhythmias). Thus a further line of enquiry seeks to determine why these problems occur and how new drugs might best be designed to prevent them. In addition, groundbreaking research is looking at the brain to provide novel genetic clues for potential causes of hypertension.

Due to our ageing population and the rising tide of obesity and diabetes, the number of people living with heart disease is increasing. Changing people's diet and exercise behaviour has been found to have a dramatic impact on both preventing and treating cardiovascular diseases, although motivating people to change the habits of a lifetime still remains a challenge.

Given the scale of all these problems, it is necessary both to understand the factors that cause heart disease and then to find new ways of treating it. At the Bristol Heart Institute emphasis is placed on taking a multi- and interdisciplinary approach to the search for solutions, as illustrated in the following pages. ■

We could be sitting on a heart disease time bomb

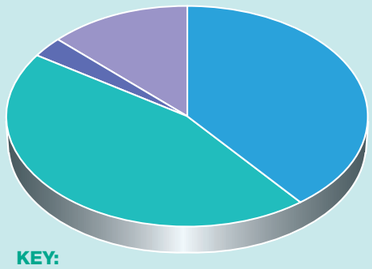
The term cardiovascular disease encompasses all disorders of the heart and circulatory system. The most common problem is coronary heart disease, which results from the furring-up of the arteries that supply the heart with blood. Deposits of fatty materials (cholesterol) accumulate in the lining of these arteries in a process known as atherosclerosis. This can lead to chest pain, or 'angina', and, more seriously, result in a heart attack.

At the Bristol Heart Institute researchers are investigating the underlying causes of heart attacks in the hope that they will be able to 'see them coming' and so take preventative steps. To this end they are improving the quality of grafts used in surgery to bypass blocked arteries, which includes the design and use of solutions that protect the heart during operations. In some forms of heart failure, the heart becomes baggy and pumps poorly, so a new operation is being tested which reduces the size of the heart, enabling it to pump blood effectively again.

Bristol Heart Institute facts & figures

people

There are over 200 personnel in the Bristol Heart Institute. They are situated within many different departments located in three University faculties, as well as in associated NHS Trusts in Bristol.



KEY:

- **13%** NHS
- **39%** **Faculty of Medical and Veterinary Sciences** Biochemistry, Pharmacology, Physiology
- **45%** **Faculty of Medicine and Dentistry** Clinical Science at South Bristol, Community Based Medicine, Social Medicine
- **3%** **Faculty of Social Sciences and Law** Exercise and Health Sciences

funding

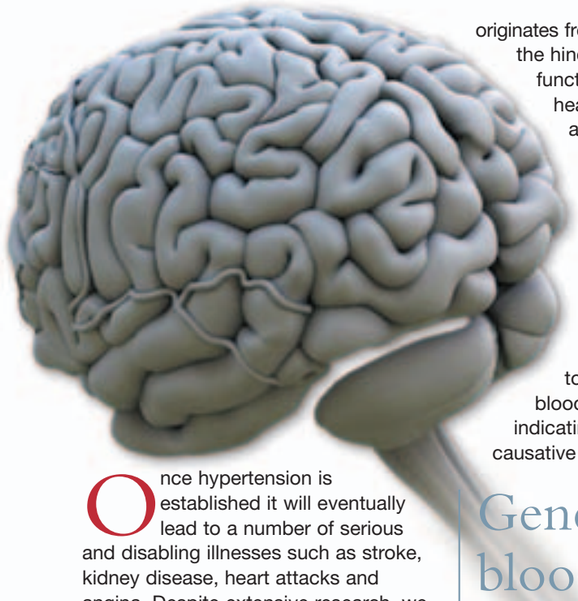
Currently the Bristol Heart Institute has a total grant income of about £54 million (from over 160 separate grants)

publications

Researchers at the Bristol Heart Institute have published over 900 original research papers since 2001

Bursting the bubble

Known as the ‘silent killer’ because it develops without us knowing, high blood pressure – or hypertension – is one of the world’s biggest killers, affecting one in three of us.



Once hypertension is established it will eventually lead to a number of serious and disabling illnesses such as stroke, kidney disease, heart attacks and angina. Despite extensive research, we still do not know what causes hypertension in 95% of suffers.

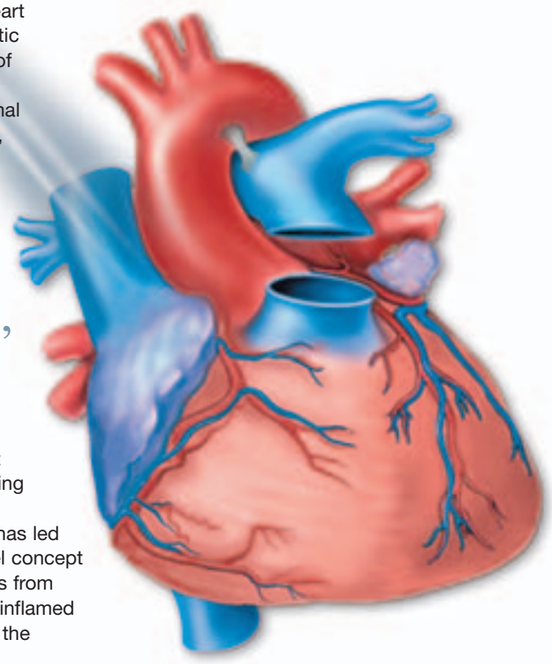
Worryingly, more than two thirds of people taking anti-hypertensive medication continue to have a blood pressure reading above the normal limit. This has prompted new investigations by a group of researchers at the Bristol Heart Institute into how the body regulates blood pressure and what can be done to control it in conditions of hypertension.

You don’t feel hypertension, so why worry about it?

Whilst obesity, diet, lack of exercise, genetic (hereditary) factors and emotional stress may all contribute to the development of hypertension, recent evidence indicates that excessive nerve activity from the brain may also be a potential cause. In healthy people, blood pressure is regulated by nervous activity that originates from specific regions of the hind brain, or brainstem. Its function is to accelerate the heart beat and narrow the arteries, thereby increasing arterial pressure during conditions of exercise and stress, for example. However, this activity becomes greatly exaggerated in people with hypertension. Interestingly, this nervous activity appears to be raised *before* high blood pressure fully develops, indicating that it may be a causative mechanism.

Genetic changes in the brain’s blood vessels may contribute to high blood pressure

Researchers in the Bristol Heart Institute have identified genetic differences in the brainstem of hypertensive subjects, when compared to those with normal blood pressure. What’s more, they have been able to show that some of these genes can cause hypertension when they are activated in the brainstem.



Many of these genes are associated with the cells that line the blood vessels supplying the brainstem and cause an inflammatory response. This has led to the emergence of the novel concept that the diffusion of molecules from these genetically altered and inflamed blood vessels directly affects the activity of brain cells that normally regulate blood pressure. These molecules are highly reactive and potentially damaging to brain cell function and appear to cause hypertension. This is an exciting new finding as now the blood vessels within the brainstem provide a novel target for treating with new drugs and possibly gene therapy strategies.

The idea would be to reduce the production of inflammatory related molecules to rescue normal brain cell function. These findings may provide a much-needed and more powerful way to bring blood pressure back down to normal, safe levels. ■

Exercise and the heart

Physical activity, nutrition and positive minds

Working out the relative importance of factors that affect the development of, or recovery from, cardiovascular disease in different ethnic, age and socio-economic groups, requires large-scale studies. The European Youth Heart Study, for example, endeavours to understand the factors that influence children’s cardiovascular risk, with the aim of identifying appropriate targets for intervention.

Extensive tests were carried out on 5,000 children (aged 9-15 years) across five different countries. Tests included blood analyses, measures of physical activity, fitness, diet and body composition. Children were given accelerometers that measure both amount and intensity of activity. Early results, already presented to the UK government and to the World Heath Organization, particularly support initiatives to encourage active travel to school.

Heart-healthy grocery store tours

Although there are guidelines available on healthy eating, it isn’t always easy to put them into practice. So, when recommending that people eat five portions of fruit or veg a day, it’s very helpful to demonstrate what a portion looks like. Similarly, when talking about the cardioprotective effects of oily fish, it helps to look at choices available and how you might cook them.

To address these issues, nutrition-education sessions ‘with a difference’ were arranged to take place in a supermarket. People with high blood lipid levels or type II diabetes, both high-risk factors for development of coronary heart disease, were taken round their local supermarket by a qualified nutritionist. The tour members selected foods they would normally buy, looked at the nutritional content, and then tried to find healthier alternatives. As one tour member put it: *“My eyes were completely opened; I’ve had diabetes for 30 years and thought I knew everything about eating healthily.”* ■

Predicting your risk of cardiovascular disease

Epidemiologists look for causes of common diseases such as cardiovascular disease in order to improve population health. One of the hardest problems they face is recognising just what the major risk factors are, and whether spurious causes have been wrongly identified as real risks.

For example, one protein found in blood – C-reactive protein (CRP) – is associated with an increased risk of cardiovascular disease, so some researchers have suggested that drug companies should search for drugs to reduce CRP levels. But epidemiologists in Bristol have questioned whether such treatments would be beneficial. Because CRP is influenced by lifestyle factors such as smoking, diet and exercise, it is impossible to tell whether CRP causes cardiovascular disease, or whether these other risk factors are the real culprits. If CRP is not a cause of cardiovascular disease, then treatments to lower it will not be beneficial.

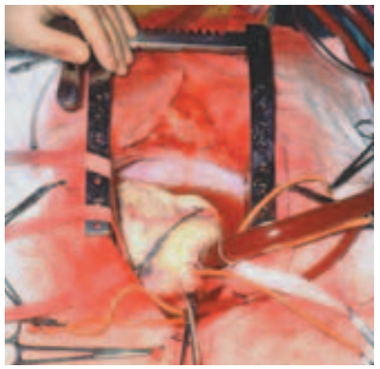
Bristol’s epidemiologists have developed a novel approach to sorting out the wood from the trees. Because CRP is a protein, it is encoded by genes. The fact that genes are fixed before birth and randomly allocated can therefore be exploited. Some people have genes that cause naturally high levels of CRP, while others have low or medium levels, but the proportion of people who smoke, take no exercise or have a bad diet will be similar in each of these genetic groups. Using this technique, researchers have shown that CRP is not causally related to high blood pressure. These important results thus allow the search for the real culprit to continue. ■

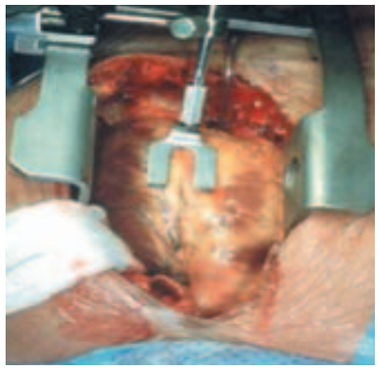
IMAGE COURTESY OF MIKE SHEIL & BRITISH HEART FOUNDATION

Mending a broken heart: innovations in cardiac surgery

Below left: Conventional 'on-pump' surgery where the heart is 'paralysed'.

Below right: Beating heart 'off-pump' surgery using a clamp.





The Bristol Heart Institute is internationally famous for its pioneering developments in the field of cardiac surgery.

Keep the heart beating

During surgery the heart is normally paralysed by a cardioplegic solution, while blood is diverted from the vascular system and pumped through plastic tubing outside the body. This artificial pump temporarily performs the functions of the heart and lungs during surgery so circulation of the blood continues, ensuring that body tissues, particularly those of brain and other vital organs, remain alive. This type of surgery is known as 'on-pump' surgery.

For many years on-pump surgery has represented the gold standard in restoring coronary blood vessel function – during vein-graft operations, for example, where a piece of leg vein is used to bypass a blocked artery in the heart. But when compared with 20 years ago, patients referred for such bypass surgery today are older, have a higher incidence of infections after surgery, greater severity of coronary heart disease, and more frequently require urgent or emergency procedures.

On-pump surgery in these high-risk groups is associated with high complication rates, substantially increased death rates and increased costs. But in 1995 a new technique was pioneered in Bristol – beating heart surgey. This required the development of a special clamp to keep a small part of the heart still so the surgeon could operate on that part while the rest of the heart kept beating. This is known as 'off-pump' surgery, since there is no need for the artificial pump. Clinical trials confirmed that short-term benefits to patients were much better if the heart did not have to stop beating – there were fewer post-surgery complications such as infections due to inadequate clearance of fluid from the lungs and temporary kidney failure as well as less blood loss and transfusion requirement, and reduced damage to the heart muscle itself.

Monitoring long-term outcome for these patients (survival rates and quality of life), and the provision of training for cardiac surgeons in off-pump techniques are now under-way to determine whether off-pump surgery performed on the beating heart will supersede conventional surgery.

Reshaping the heart

Heart failure commonly results from inadequate blood supply to the heart, due, for example, to atherosclerosis. If severe enough, the heart muscle cells will die in the area originally ➜ supplied by the atherosclerotic vessel. The dead cells are replaced with scar tissue, the size of which varies according to the amount of damage.

The presence of this scar tissue initiates a vicious cycle of events. The heart gradually gets bigger, resulting in a gradual reduction of the overall heart pumping function and increased strain on the walls of the heart, with a stretching effect on the remainder of living heart cells. Patients with this condition have hearts that are about twice normal size. Whilst various drugs can restore heart function to some extent, none can address the basic problem – that the heart has become too big for it to work properly.

Using a new procedure of 'left-ventricular reshaping surgery', surgeons at the Bristol Heart Institute have pioneered a new way to cut through the scar tissue to enter the heart. They then pull the remainder of the good muscle together, effectively removing the large scar from the pumping part of the heart. They can then use the scar tissue as a firm surface to sew onto, to close the heart cavity. This restores the heart's normal shape, releases the remaining muscle from the stretching effect of the scar, and so allows the remaining living heart cells to regain their pumping effectiveness. In just a few months this produces rapid and dramatic improvements in heart function and hence in patients' quality of life.

But, like all new operations, it has to be proved to be beneficial over current therapies. A major international effort is ongoing, with cardiovascular centres in 15 countries participating – the first study of its kind in this field of research. It will provide evidence as to whether a reduction in left ventricular volume improves survival, and whether it is able to revert or stop further heart enlargement. Hopefully this technique will prove as beneficial as initial results suggest.

Recovery after cardiac surgery

Anaesthesia and the trauma of surgery cause inflammation, which stimulates the patient's immune system and wound-healing defence mechanisms. This is essential for recovery, but any abnormality in the inflammatory response can cause infections that may lead to septicaemia (blood poisoning). A wide variation is seen in individuals' response to infection and recovery after surgery, and researchers are investigating whether a person's genetic make up may explain this.

It has even been proposed that patients could carry a silicon chip containing their genetic profile by the year 2010. Such technology could provide individually targeted therapy and improve clinical outcome after surgery. ■

Growing a new heart?

In surgery that reshapes the heart it may be possible to further improve heart function by replacing the dead or damaged heart cells with new ones. A problem with this is that, unlike cells in some other organs of the body, heart cells cannot divide to produce new ones. However, certain cells called stem cells have the potential to develop into any other kind of cell, including heart cells.

In adults, stem cells are found in a few organs and bone marrow. So a patient's own bone marrow could potentially be used to provide stem cells to replace damaged heart cells. But only a small fraction of adult stem cells can transform into heart cells, and the process is not very efficient.

Recent research at the Bristol Heart Institute suggests that embryonic and foetal stem cells may be much more potent in stimulating growth and repair of the heart than adult stem cells. But use of embryonic and foetal tissue is controversial and raises ethical issues.

Experts in Medical Ethics at the Bristol Heart Institute are actively looking at issues surrounding the use of stem cells, especially the implications of current European legislation. The UK government's present position is that research using all sources of stem cells should be supported, because: "Currently it is too early to know where the most useful findings will come from".

Professor Gianni Angelini (right) receiving the award for Best Surgical Team of the Year 2005.

Keeping to the heart beat

During each heart beat a small amount of calcium enters each of the muscle cells that make up the heart. This activates a large, rapid release of calcium from a store inside the cell that then activates cell contraction.

Heart cells are surrounded by a surface membrane. This does not form a smooth surface but has invaginations in it (known as t-tubules) which penetrate deep into the cell and hence greatly increase the surface area. Calcium can only enter cells through specific, tiny, channels, which are found mainly in the t-tubules. Transport of other ions, like sodium and potassium, occurs through different channels contributing to the regulation of heart contraction. Abnormalities in the transport of any of these ions can lead to potentially fatal disturbances in the normal cardiac rhythm – so called 'arrhythmias'.

Synchronised contraction of millions of cells causes the heart to beat

By using biophysical, biochemical and molecular biological techniques, it is possible to study how changes in the mechanisms that regulate these ion channels can lead to the development of arrhythmias and other types of heart disease. For example, in heart failure, contraction of the heart is much weaker than normal, causing blood to be pumped less effectively. This is due partly to less calcium entry into the cell because of changes in the function of ion channels, which may be at least partly due to the cells having fewer t-tubules.

Single heart cells:

Top: Normal cell stained green to show t-tubules.

Bottom: Cell lacking t-tubules.

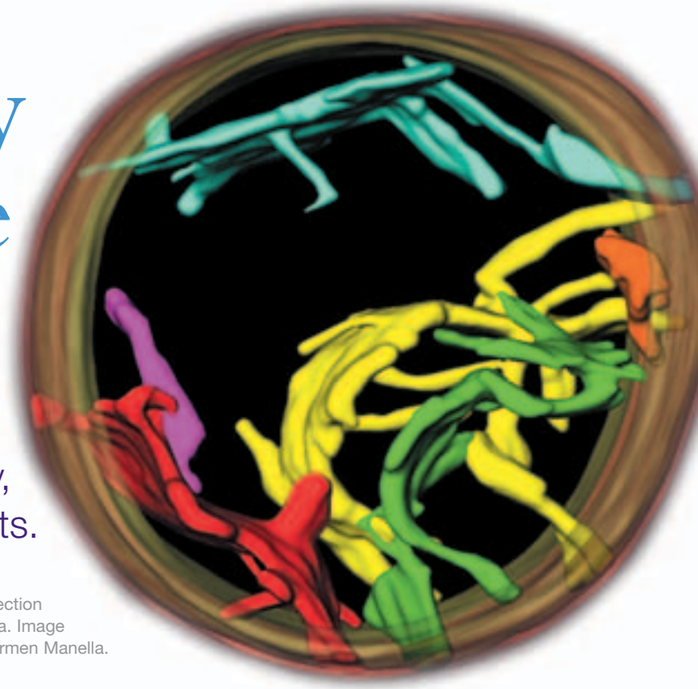
that researchers at the Bristol Heart Institute are now trying to answer is how the structure and function of this particular ion channel makes it susceptible to being blocked by such drugs. Answers to this problem are clearly important for the future design of safe drugs.

Interestingly, there are major differences between men and women in the likelihood of their suffering serious cardiac arrhythmias – women are more susceptible to arrhythmias due to long QT syndrome, whereas men appear to be more susceptible to arrhythmias arising from abnormal function of other ion channels. But astonishingly little is known about the mechanisms that cause these gender differences. It seems probable that they arise from the actions of the different sex hormones – testosterone and oestrogen – on the heart. Investigating the role of the sex hormones in modifying cardiac ion channel behaviour should uncover the basis of these sex differences in the susceptibility of the heart to arrhythmias. In turn, this will allow the development of drug therapies that are equally safe for both men and women. ■

Major differences in men's and women's cardiac arrhythmias

Activity of ion channel behaviour that may lead to arrhythmias can be detected by an electrocardiogram (ECG). Increased risk of one particular type of arrhythmia is caused by impairment of a potassium channel – the 'HERG' channel – which causes a change picked up by the ECG known as 'long QT syndrome'. Surprisingly, a number of drugs in routine use for non-heart related problems were found to cause this abnormality, so these were subsequently withdrawn. The drugs acted by blocking the HERG channel. A key question

The energy powerhouse



The heart beats over 100,000 times a day, pumping about 20 thousand litres of blood around the body, delivering oxygen and nutrients.

This requires a lot of energy, and the 'power stations' within heart cells that make the energy are called mitochondria. They convert energy from food into chemical energy – adenosine triphosphate (ATP) – in a process that also uses oxygen. Researchers at the Bristol Heart Institute are looking at mechanisms that regulate ATP supply normally, in order to find out what goes wrong in some types of heart disease when mitochondria cannot make enough ATP.

ATP levels can now be measured in living heart cells using the protein luciferase, which is naturally found in the tails of fireflies. Luciferase lights up in the presence of ATP, which is what causes the tail to glow, since fireflies use ATP to power flight. By transferring luciferase into heart cells which then 'light up', the levels of ATP can be observed and the mechanisms controlling its production determined.

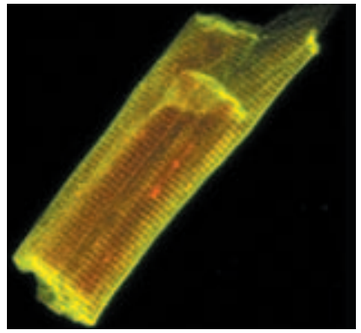
The light is recorded using a microscope and a highly sensitive camera. Conditions causing oxygen deprivation to the heart, like angina, coronary heart disease and also cardiac surgery, prevent enough ATP being made. Even worse, when the blood flow to the deprived (ischaemic) heart is restored, mitochondria can change from being energy providers to killers that cause irreversible damage to the heart. Research directed towards elucidating the mechanism responsible for this 'Jekyll to Hyde' change in the behaviour of mitochondria aims to develop ways of preventing it occurring. Some of the drugs that do this now show potential for use during cardiac surgery.

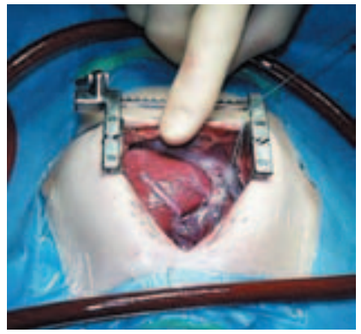
Right: Cross section of mitochondria. Image courtesy of Carmen Manella.

The energy solution

During open heart surgery, blood is diverted away from the heart using a bypass machine that keeps blood pumping around the rest of the body, but this can damage the heart muscle. To minimise this damage, cardioplegic solutions are infused into the heart that stop the heart beating, both saving its energy and allowing surgeons to operate on it.

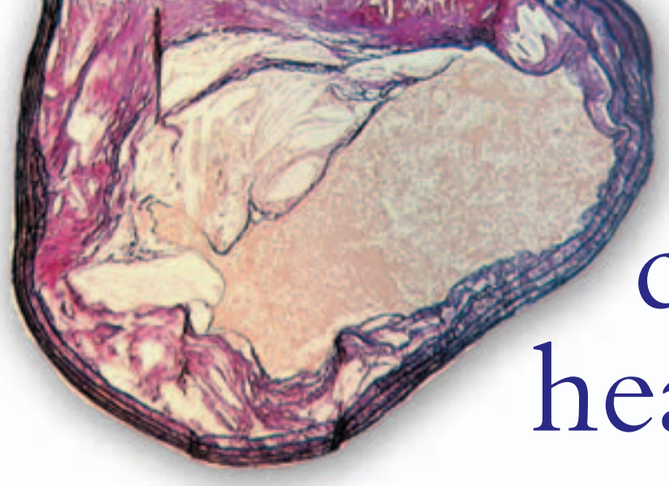
Research has shown that supplementing the cardioplegic solutions with agents that preserve the heart's ATP supply can also protect the heart during surgery. This was demonstrated by collecting (very small) heart muscle biopsies and blood samples during surgery. These samples were used to measure the ATP reserves in heart cells, as well as proteins that are released from the heart into the blood when heart cells die. Monitoring these markers enabled the design of improved cardioplegic solutions, including use of warm solutions (cold solutions had previously been used), and solutions supplemented with blood. Another finding was that the solutions had to be designer-made for different age groups and different types of heart disease. A challenge facing paediatric surgeons is the small size of children's hearts, so they need optimum protection during surgery. As one surgeon put it: *"These significant improvements for patients undergoing heart surgery are an excellent example of how basic science and clinical research can complement each other to change clinical practice."* ■





Above: Individual heart cell stained for a protein involved in energy metabolism.

Bottom: Paediatric heart surgery.



Plaques, cracks and heart attacks

There are about 1.3 million people in the UK who have survived a heart attack. But they are the lucky ones, since a third of all heart attack victims die before reaching hospital.

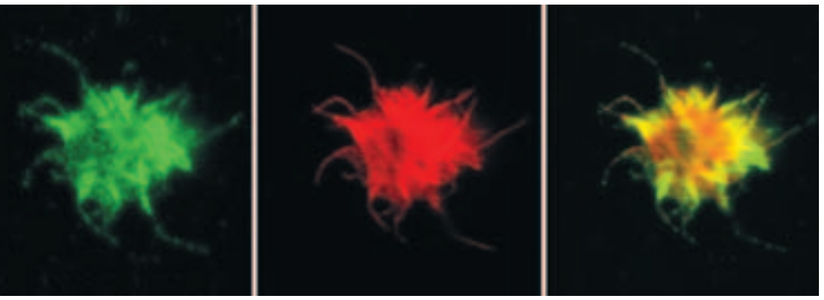
Atherosclerosis involves the slow build-up of fatty material, white blood cells and connective tissue inside an artery wall, to form a 'plaque'. If the plaques are sufficiently large to prevent adequate blood flow to the heart, patients experience angina. More devastatingly, though, some plaques are unstable and can crack (rupture). This attracts blood cells called platelets that within minutes form a clot in the artery – the most common cause of a heart attack.

What causes plaque rupture?

Atherosclerotic plaques are normally stabilised by a fibrous 'cap', consisting of smooth muscle cells that produce strengthening proteins like collagen. But the fibrous caps also contain enzymes, known as matrix metalloproteinases (MMPs), that can degrade collagen, so they could potentially cause plaque rupture.

Conversely, plaque rupture could be prevented by increasing the number of smooth muscle cells in the fibrous cap so that it doesn't crack.

So a major research focus of the Bristol Heart Institute is elucidating the role of the MMPs and the mechanisms causing smooth muscle cell growth in order to understand plaque rupture. Until recently this was difficult, owing to the lack of suitable experimental models. But now researchers have developed a unique model using mice that produce unstable plaques in their arteries after eight weeks on a high-fat diet. Experiments were conducted in mice, each with a different MMP 'knocked out'. Knocking out some MMPs made plaques more stable, as expected; however, other MMP knock-outs actually made plaques more fragile, implying that these played a particular role in plaque stability instead. These findings caused a major pharmaceutical company to refocus its MMP-related drug development programme.



But cells in the atherosclerotic plaque secrete enzymes other than MMPs that can contribute to plaque rupture. Researchers are therefore using methods that scan all the genes expressed in plaque cells to find out what makes a plaque unstable. If genes could be found that serve as markers in blood to indicate whether someone has an unstable plaque, then that patient could be treated before suffering a heart attack.

Guarding against thrombosis

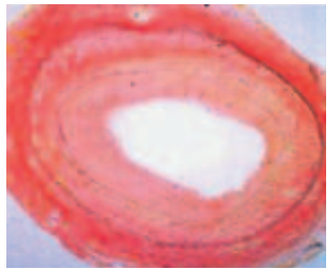
Central to thrombosis are platelets, the smallest cells in the blood, whose normal role is to stop bleeding. Platelets are very active and sticky, although their ability to stick together is regulated by events inside the cell, known as a signalling pathway. This signalling involves enzymes called protein kinases that eventually trigger clotting. One of these enzymes, protein kinase C, seems particularly important in this process, and researchers are investigating whether protein kinase C can be used as a novel target to prevent blood clotting following, for example, rupture of atherosclerotic plaques. ■

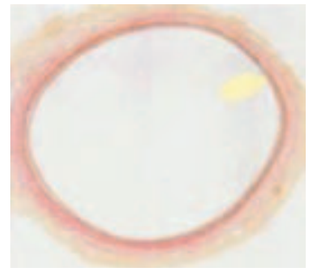
Top left: Cross section of an artery that has become blocked due to plaque rupture.

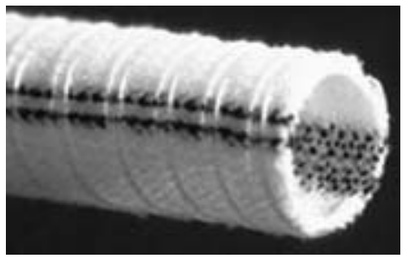
Left: A single platelet stained for different proteins involved in blood clotting.

Building a bypass to last

Coronary heart disease involves a long-term furring-up of the coronary arteries that develops over many years. Coronary artery bypass grafting remains the most effective treatment of this condition.







Above left: Cross section of vein a few months after grafting.

Above right: This vein has had the Extent placed around it before grafting (wall is much thinner, so more room for blood to flow through).

Left: Extent – sheath placed around the leg-vein before use in the heart.

A heart bypass generally involves taking a piece of vein from the patient's leg and bypassing the blocked segment, restoring blood flow to the heart and reducing the risk of heart attack (infarction). Unfortunately, less than half of these vein grafts are still working after 12 years of use. The vein does not seem to adapt well to its new role as an artery and wall thickening occurs due to smooth muscle cell growth of the vein wall, or the new vein itself furs up. Although arteries (from mammary glands) are increasingly used and seem to adapt better, the one million operations completed each year still use about two million vein segments.

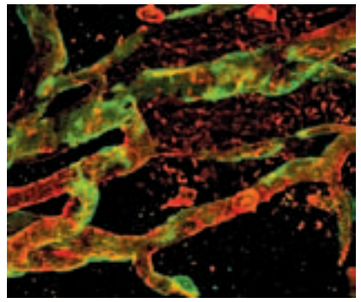
> The vein does not adapt well to its new role as an artery

So prolonging the lifespan and quality of the vein graft has been an area of intense investigation by researchers at the Bristol Heart Institute for several years. They have found that covering the vein graft with a porous Dacron sheath, called the external stent or 'Extent', prevented wall thickening almost completely in experimental models. Over the ensuing years the basis for this effect has been better understood and the design of the stent so enhanced such that a randomised clinical trial of the Extent in patients having bypass grafts has recently started at the Bristol Heart Institute.

Thickening of the veins is caused mainly by smooth muscle cell growth (the cells in the graft divide and multiply), so drugs that prevent this may also prevent vein thickening. Promising pre-clinical studies have focused on the use of drugs that have a potent ability to prevent smooth muscle cell growth, such as drugs commonly used in the treatment of cancer or transplant rejection. These have been shown to inhibit vein-graft disease in experimental models. Future research in this area is directed at refining drug delivery with the hope that these drugs may be entered into clinical trials in the next few years. Finally, a (non-harmful) virus has been engineered to introduce a gene called TIMP-3 that not only reduces movement of smooth muscle cells to the vein wall, but also destroys those already present. Local application of this virus has reduced vein-wall thickening and it is anticipated that human trials could start within a few years.

Can the heart grow new blood vessels?

One method of improving blood supply to the heart that does not involve surgery is to get the heart to grow its own new blood vessels – a process known as angiogenesis. Certain genes encode proteins called growth factors that can stimulate formation of new blood vessels. Recent research, using experimental models, has shown that injection of such genes can stimulate angiogenesis. However, to achieve that, genes for several different growth factors are required, since they stimulate different parts of blood vessel development. Some growth factors stimulate vessel 'sprouting', whilst others cause support cells to surround the newly growing vessel, before being replaced finally by smooth muscle cells. Researchers at the Bristol Heart Institute are investigating which combination of these growth factors is most beneficial. ■



Growth factors stimulate new blood vessel formation.

We would be capable of nothing without the continued support of our sponsors. We would therefore like to thank the following for funding our research:

British Heart Foundation
Wellcome Trust
Garfield Weston Trust
Medical Research Council
Heart Research UK
Biotechnology and Biological Sciences Research Council
Association of International Cancer Research
Cancer Research UK
Diabetes UK
Kidney Research UK
National Institute of Health
The Royal Society
Scottish Scientific Office
Stroke Association
Juvenile Diabetes Foundation International
EU Community
BUPA Foundation
AstraZeneca
Edwards Lifesciences
Merck
Organon Laboratories Ltd
Pfizer
Procter & Gamble
Sorin Biomedical

re: search

Public Relations Office
Communications & Marketing Services
University of Bristol
Senate House
Tyndall Avenue
Bristol
BS8 1TH

www.bristol.ac.uk

LEARNING • DISCOVERY • ENTERPRISE