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BHF Research Unit: Cardiovascular Remodelling

The BHF Research Unit at Leeds has currently two major research themes.

Cardiac Magnetic Resonance (CMR)

A comprehensive MR protocol for the assessment of ischaemic heart disease (IHD) has been developed over the last five years, concentrating particularly on perfusion and viability. The clinical utility of CMR in the investigation and management of IHD is being investigated in a 750 patient study supported by a BHF programme grant. Recruitment will complete in Aug 2009. A new 3T CMR facility will open in 2010 supported by a BHF infrastructure grant and the University. Key group members are John Greenwood and Sven Plein, with David Buckley and John Ridgway from Medical Physics.

A
B
C
D

Column A = Late gadolinium-enhancement CMR in the short axis.
Column B = Rest perfusion CMR at peak myocardial enhancement in the identical location.
Column C = Adenosine stress perfusion CMR with identical image parameters to column B.
Column D = Corresponding X-ray coronary angiogram.

Cellular & Molecular Cardiovascular Remodelling

A major interest is in understanding the mechanisms of how cardiovascular tissues remodel in disease. Key group members are Chris Peers (hypoxic regulation), Karen Porter (extracellular matrix regulation), Neil Turner (signal transduction), Justin Ainscough (gene modification), Jason Scruggs (viral gene transfer), Mark Drinkhill (murine pathophysiology), Azhar Maqbool (genetic regulation).


Funding:
British Heart Foundation (BHF)
Medical Research Council (MRC)
Wellcome Trust

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Ball_SG/

Representative publications
Neurochemical Mechanisms of the Neural Pathways of Cardiovascular Control

Our goal is to use neuroanatomical, immunohistochemical and molecular biological techniques to elucidate the neurochemical mechanisms of the neural pathways of cardiovascular control, from the peripheral receptors and effectors in the heart and cardiovascular system to the central neurones relaying and integrating the signals in the brain stem. Such basic knowledge will aid the development of new therapeutic strategies for treating hypertension and circulatory diseases, and also shed light on how existing treatments affect the neural regulation of cardiovascular function. Although the basic neuroanatomy of the reflex pathways controlling the heart is now understood, as are many of the neurotransmitters involved, it is evident that there are complex neuronal circuits operating within the brainstem, in particular the nucleus of the solitary tract (NTS), using a vast array of potential transmitters that are still to be characterised, as are the mechanisms by which neural projections from other areas of the CNS interact with them to modulate cardiorespiratory control. We know for example that inputs from "higher" areas of the CNS such as the amygdala and hypothalamus can modulate the activity of neurones in the NTS but know little about the transmitter mechanisms involved. By identifying neuronal pathways using tracers such as cholera toxin B (CTb) combined with immunohistochemistry we have demonstrated projections from the amygdala containing GABA and somatostatin, and projections from the spinal cord containing glutamate and substance P.

We are using antibodies, together with in situ hybridisation and polymerase chain reaction probes to further investigate the neurochemical coding of the synaptic connections involved and to localise and quantify changes in the expression of the receptors and transporters for transmitters, peptides and steroid (oestrogen) receptor subtypes that may underlie modulatory actions on the central cardiovascular neuronal circuitry in hypertensive animal models.

In the course of this objective, we hope to take advantage of relevant new developments in imaging techniques, sub-cellular probes and animal models.

Collaborators: D.V. Pow, Queensland, Australia
M. Garret, Bordeaux, France

Funding: British Heart Foundation

More information: http://www.leeds.ac.uk/medhealth/light/staff/batten_t.html

Representative publications


Corbett EK, Mary DA, McWilliam PN, Batten TFC. (2007). Age-related loss of cardiac vagal preganglionic neurones in spontaneously hypertensive rats. Exp Physiol. 92, 1005-1013

Ion Channels and Vascular Disease

My research group focuses on the roles of ion channels and new strategies for drug development. Facilities include high-throughput calcium measurement and automated planar patch–clamp systems. Blood vessels direct oxygen and nutrients to every organ, and even tumours. These complex structures can go wrong and cause disease. A very high proportion of us will die or be disabled because vascular disease. Other diseases – such as Alzheimer’s disease – may also originate in blood-vessel abnormalities.

The laboratory works particularly on the predominant cell type of most blood vessels – the smooth muscle cell – and on a specific set of proteins within these cells, called ion channels. We discover novel ion channels and associated mechanisms and then test their relevance to the function and disease of human blood vessels by working, for example, with cardiothoracic and vascular surgeons (Figure 1).

One ion channel discovered to have a role in blood vessels is TRPC. This type of protein was originally discovered in the visual system of the fruit fly, but other wider functional roles have clearly evolved. To facilitate exploration of the roles of such ion channels we developed E3-targeting methodology (Figure 2). Such E3-targeted reagents have important utility for drug-target validation, and potentially as direct therapeutic drugs. The reagents were used in our study revealing TRPC channel activation by extracellular redox protein.

TRPC is part of an ion-transport system regulating smooth muscle cells during adaptive and disease processes. Switching on of other ion channels during such events goes hand-in-hand and we have been intent on discovering the underlying switching mechanisms.

We made a breakthrough in showing the role of the REST transcription factor, a protein controlling the expression of a specific potassium channel gene.

Representative publications


Funding:
Wellcome Trust, British Heart Foundation

Overseas collaborator: Katsuhiko Muraki (Japan)

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Beech/
Computational modelling of normal and hypertrophic cardiac electromechanics from diffusion tensor imaging and histology

Individuals with cardiac hypertrophy have a significantly increased risk of ventricular fibrillation, an often fatal arrhythmia. Computational cardiac models (Figure 1) provide tools for examining the mechanisms underlying the onset of such arrhythmias and interventions aimed at either preventing this onset or restoring normal sinus rhythm, as the data they provide can be dissected in time and space, and by parameters. The aims of my research are to develop biophysically detailed, contracting electromechanical continuum models of the ventricles, and use these models to evaluate the mechanisms of ventricular fibrillation development in hypertrophy, and the electromechanical consequences of such an arrhythmia.

Diffusion tensor magnetic resonance imaging (DT-MRI) is used to obtain libraries of normal and hypertrophic ventricular geometries and architectures. DT-MRI gives diffusion tensors throughout a tissue, from which can be computed fibre and sheet orientations along with tissue anisotropies. Electrophysiological heterogeneities throughout the ventricular myocardium are mapped using histology and immunohistochemistry. Analysis of these data reveals the inter- and intra-species variations in the organisation of the cardiac architecture, and the spatial distribution of the electrophysiological heterogeneities.

Biophysically detailed electromechanical continuum models of the ventricles are then developed that incorporate spatially heterogeneous membrane excitation, excitation-contraction coupling and normal/abnormal intracellular calcium dynamics, the resultant deformation, and mechanoelectric feedback, with both normal and hypertrophic excitation and contraction parameters, geometries and architectures. The models describing electrophysiology are high order systems of nonlinear ordinary differential equations to simulate excitation in cells, or reaction-diffusion partial differential equations to simulate propagation through tissue. The mechanics and deformation of the heart are described by continuum mechanics and modelled using finite element methods. The geometries and architectures of the developed models are extracted from the libraries obtained using DT-MRI. Simulation, visualisation and analysis of ventricular fibrillation in hypertrophy is carried out on high performance computing resources utilising novel parallelisation and integration methods.

The models describing electromechanics from diffusion tensor imaging and histology

Funding: Medical Research Council, Multidisciplinary Cardiovascular Research Centre

More information: http://www.cardiovascular.leeds.ac.uk/staff/Benson_A/

Representative publications
Three-Dimensional Organisation of Cardiac Electrical Activity during Arrhythmias

My research focuses on the mechanisms underlying life-threatening cardiac arrhythmias leading to sudden cardiac death, the largest cause of death in the industrialized world.

Every heartbeat is triggered by electrical waves of excitation propagating through the cardiac muscle from sinus node to the ventricles. Abnormal propagation of this wave severely compromises the mechanical function of the heart and represents a major cause of arrhythmias. Re-entry, during which a wave of excitation repeatedly activates the cardiac muscle, is such a type of abnormal propagation and occurs during dangerous arrhythmias such as fibrillation. My laboratory utilizes both computational and experimental techniques to visualize the propagation of electrical waves through myocardium and understand the mechanisms underlying re-entry and associated arrhythmias.

There is compelling clinical evidence that acute myocardial ischemia occurring after coronary occlusion is one of the most important causes of ventricular arrhythmias. Recently, we discovered a novel mechanism for arrhythmogenesis during early regional ischemia using a realistic computational model of ischemic myocardium.

In this model, re-entry occurred as a result of calcium-mediated alternating conduction blocks in the ischemic border zone. Based on this hypothesis, we have designed an experimental model of regional ischemia and are currently investigating arrhythmogenesis in this model.

Optical imaging using voltage-sensitive dyes has become a powerful tool to study electrical propagation in cardiac tissue. However, poor transparency of tissue has enforced surface or sub-surface imaging and prevents the use of conventional optical methods to visualize the electrical waves through the thickness of the cardiac muscle.

My laboratory works on the application of novel optical tomographical methods and laser scanning to probe deeper layers of the cardiac muscle and unravel the three-dimensional wave patterns underlying cardiac arrhythmias.

Funding: Research Foundation – Flanders (Belgium), IWT (Belgium)
Collaborators: Arkady Pertsov (USA), Sasha Panfilov (The Netherlands), Henri Verschelde (Belgium)
More information: http://www.cardiovascular.leeds.ac.uk/staff/Bernus_O/

Representative Publications
Control of signalling in the cardiac cell

The heart pumps blood around the body, delivering nutrients to and removing waste products from every organ. Its function is finely tuned to respond to the demands of the body. My research focuses on the mechanisms which control the behaviour of individual cardiac muscle cells in the heart in response to a variety of stimuli. This information can be used to understand the function of the heart in both health and disease.

The way that the heart functions in a healthy individual is a result of a balance between the stimulatory sympathetic nervous system and the inhibitory parasympathetic system. These 2 systems work through different receptors (β-adrenoceptors and muscarinic receptors), but both signal through the second messenger cAMP. I am interested in how cellular signalling is controlled to allow these receptors to produce such diverse functional responses. One structure that contributes to this is the caveola, which is a small flask shaped pocket in the cell membrane (Figure 1).

Caveolae can concentrate or exclude components of signalling pathways so as to modulate both the efficiency and fidelity of signal transduction. Our recent work has shown that caveolae are responsible for compartmentalising cAMP signals in the cardiac cell. Cholesterol-rich caveolae are a potential target for statins and, through cAMP, this may have consequences for the contractile reserve of the failing heart.

The heart possesses a unique intrinsic ability to regulate its force of contraction in response to circulatory demand. For example, during exercise, the amount of blood returning to the heart increases and stretches the cardiac muscle. This acts as a stimulus for increased contraction, allowing the chambers of the heart to expel this greater volume of blood. Some of the processes which link stretch to increased contraction are not understood.

I have identified a number of elements (stretch-activated channels, the NaH exchanger) which contribute to the slow phase of force increase following stretch both in single cardiac myocytes. My current work explores the role that caveolae, which could act as reservoirs of extra membrane recruited upon stretch, play in the mechanotransductive response of the heart.

Cardiac function is adversely affected by many different diseases. For example, cardiovascular complications are a major cause of disability and death in patients with diabetes. We have recently made a novel finding that changes in the microtubules, a network of hollow fibres (Figure 2), contribute to adverse alterations in cardiac cell function in a model of type 1 diabetes.

Funding:
British Heart Foundation; MRC; Heart Research UK; Royal Society.

Overseas collaborators:
Robert Harvey (Nevada); Jean-Yves Le Guennc (France); Chris Howarth (UAE)

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Calaghan_SC/

Representative publications


Phenotypic modulation of ion channels

The laboratory is interested in understanding the regulation of the changes occurring when a cell differentiates into a different phenotype. An example of such changes is the expression of ion channels—membrane proteins which allow the flow of ions such as calcium and potassium. Small changes in channel expression can lead to dramatic changes in cell integrity and function, causing cells to proliferate or to become cancerous. Our data show two ion channels crucial for proliferation. These two channels are “switched on” through transcriptional de-repression by a transcription factor called ReSt (repressor element 1 transcription factor). ReSt is lost in proliferation by as-yet undetermined mechanisms, leading to the upregulation of ion channels and cell proliferation. Current projects in the laboratory investigate the changes in and the modulation of ion channels occurring in vascular proliferation and in lung cancer progression.

Vascular proliferation

Vascular proliferation occurs in the creation of new blood vessels, and unfortunately also during coronary artery disease. This is when the arteries supplying blood to the heart muscle become hardened and narrowed due to excessive proliferation of smooth muscle cells (see Figure 1). Blood flow to the heart is reduced, starving the heart muscle of oxygen with increased risks of cardiac arrest.

In collaboration with cardiac surgeons at the Leeds General Infirmary, we have made several important discoveries, especially in identifying key proteins involved in vascular proliferation in a human disease context, namely the transcription repressor REST. What controls REST is an important area of research for understanding smooth muscle physiology and ultimately its role in cardiovascular disease, for which I am funded by a British Heart Foundation Intermediate Fellowship.

Lung cancer progression

During the change from a normal lung epithelial cell towards cancer, a series of genetic alterations occur, which may affect the expression of ion channels or cause a change in channel activity. These abnormalities are then able to contribute to the tumour proliferation. Together with thoracic surgeons at St James’s Hospital, we have been characterising the expression of ion channels through the stages of lung cancer. Understanding this difference will further our understanding of the tumour progression and potentially make K+ channels excellent pharmacological targets for cancer therapy and biomarkers for the diagnosis of carcinogenesis.

Funding:
Royal Society, British Heart Foundation

Overseas collaborators:
Chris Howarth (UAE)

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Calaghan_SC/

Representative publications

Figure 1: Sections from a human saphenous vein before and after developing a neointimal thickening.
Natural & Therapeutic Control of Cardiac Function ion and regulation of proteases

The performance of many biological events is controlled through the transient chemical modification of components, or the partnering of new components in a cell. Where and when these events take place is key to the process of control, and errors in these processes can lead to human disease. In my lab we are interested in the development of technologies which permit observation of these short-lived chemical events, and the application of these technologies to understand normal and abnormal cardiac performance. The chemical adaptation of a small number of influential proteins changes the performance of the heart to meet the demands of exercise and stress, but this process fails following cardiac damage leading to life threatening loss of performance of the heart. We have developed tools to examine these events by immunoassay, and within the company Badrilla Ltd., we are developing quantitative immunoassays based on novel proprietary calibration standards.

We are also developing novel experimental strategies for cardiac therapy. Having identified influential components in cardiac biology, we have engineered a strategy in which the diseased component (a protein) is removed by molecular intervention and replaced with a designer version of the component which corrects the malfunction. This strategy is being developed with a cardiac protein component, but has applications across medicine & biotechnology.

Funding: MRC

More information: http://www.cardiovascular.leeds.ac.uk/staff/Colyer/

Representative Publications


Carter, S., Colyer, J., Sitsapesan, R. (2006) Maximum phosphorylation of the cardiac ryanodine receptor at serine-2809 by protein kinase A produces unique modifications to channel gating and conductance not observed at lower levels of phosphorylation. Circ. Res. 98, 1506-1513


Jim Deuchars  
BSc Physiology, iii, Glasgow (1988)  
PhD Physiology with Prof. KM Spyer, University of London (1992)  
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Central neuronal circuits influencing cardiovascular control –from  
neuronal characteristics to pathway discovery and function  

This research is a team effort, areas of which I lead in conjunction with Sue Deuchars. We investigate the organisation and function of the parts of the brain and spinal cord that contribute to control of the autonomic nervous system. This branch of the nervous system undertakes tasks to keep our body functioning, such as control of blood pressure, heart rate, breathing and digestion. The current team comprises postdoctoral and postgraduate researchers who use CNS slice electrophysiology, neuronal tracing, molecular biology, immunohistochemistry and light and electron microscopy. This interdisciplinary approach allows us to examine issues from several angles, leading to us being able to:  

•identify new CNS regions that may be involved in autonomic control, for example a nucleus in the brainstem that receives afferent input from neck muscle proprioceptors and which projects to the nucleus tractus solitarius, a region pivotal in central autonomic neurocircuitry (Edwards et al., 2007. J Neurosci. 2007 Aug 1;27(31):8324-33).  

•provide evidence that the major group of inhibitory neurotransmitter receptors, GABA receptors, can be made up components from 2 (A, C) of the 3 (A,B,C) sub-types (Milligan et al., 2004, J. Neurosci, 24:9241-50).  

•reveal the distribution and function of ion channels contributing to the properties of specific groups of nerve cells involved in autonomic neuronal circuits –both in the brainstem (Dallas et al., 2005, J.Physiol. 562:655-72) and the spinal cord (Deuchars et al., 2001, neurosci., 106, 433-446). In each area these channels appear to mark a cell type with specific roles in influencing autonomic nervous activity. In one study (Dallas et al., 2005), we applied antibodies as ion channel specific modulators to identify the specific channel proteins contributing to neuronal behaviour (see Figure 1).  

Funding: Wellcome Trust; British Heart Foundation; Government agencies MRC, BBSRC.  

More information: http://www.cardiovascular.leeds.ac.uk/staff/Deuchars_J/  

Representative publications  


Calcium signalling in the heart

My research is focused on understanding the electrical activity and mechanical function of the heart to work as an efficient pump. The heart must beat in a coordinated fashion. Cardiac muscle contraction is stimulated by electrical activity of the cardiac action potential. This complex pathway, known as excitation-contraction (e-c) coupling, can be disrupted resulting in reduced pumping efficiency of the heart and heart failure. My research focuses on how electrical activity and mechanical function of the heart are coordinated and regulated—how changes in cardiac calcium signalling under normal and pathophysiological conditions may result in heart failure and how molecular mechanisms may prevent such defects. Furthering our understanding may provide useful therapeutic targets for the treatment of heart failure.

We recently discovered regional differences in e-c coupling and calcium signalling in the heart. We also showed these regional differences in calcium signalling and e-c coupling result in differential activation of the calcineurin-NFAT pathway. This in turn causes differential expression of a cardiac potassium channel gene involved in electrical excitability of cardiac tissue. We are intent on discovering the mechanisms responsible for controlling this excitation-transcription coupling pathway, which may prove to be a ubiquitous signalling pathway of excitable tissues. (Figure 1).

Sympathetic nervous system-mediated control of cardiac function results from activation of the β-adrenergic signalling pathway and numerous downstream effector molecules. Cellular compartmentalization of the response to adrenergic signalling is in part the result of localized a-kinase anchoring proteins. Recently we demonstrated localization of adrenergic signalling to specific cardiac potassium channels. (Figure 2). We are interested in further understanding localization of protein kinase a signalling within cardiac muscle.

We recently found a rare fatal heart condition (LQT 4) can be caused by disruption of a protein (ankyrin-B) that anchors ion channels within cardiac cells. Mutation of ankyrin-B results in disrupted sub-cellular organization, altered cardiac calcium signalling and susceptibility to arrhythmia and sudden death with exercise or β-adrenergic stimulation. (Figure 3). More information: http://www.cardiovascular.leeds.ac.uk/staff/Dilly_K/
Our laboratory is concerned with reflex control of the cardiovascular system and the underlying mechanisms involved. Specialized receptor endings sensitive to either mechanical events or chemicals relay information regarding the ‘body’s internal environment’ to the central nervous system. This sensory information is integrated to bring about changes in heart rate and blood pressure. A basic knowledge and understanding of the normal regulation of the cardiovascular system is vital to interpreting the underlying causes of cardiovascular disease and from this new future treatment strategies can be targeted and developed.

Our research into better understanding the cardiovascular system involves a variety of specialized in vitro and in vivo techniques. One technique we have recently acquired is radio telemetry in small animals. Using this technique to record blood pressure and heart rate we are able to monitor over the long term the progression of heart disease in animal models and determine effective interventions.

We are particularly interested in a group of sensory nerves located around the coronary arteries able to detect changes in arterial blood pressure. These coronary baroreceptors have a number of unique features which set them apart from the classical arterial baroreceptors found in the carotid sinus and aortic arch. In particular these coronary baroreceptors do not show acute resetting and we believe may be critical in controlling mean arterial blood pressure. We currently have a collaborative study with a thoracic surgeon to determine if these receptors are damaged during cardiovascular disease.

**Funding:**
Wellcome Trust
British Heart Foundation

More information: [http://www.leeds.ac.uk/medhealth/light/staff/drinkhill_m.html](http://www.leeds.ac.uk/medhealth/light/staff/drinkhill_m.html)

Representative publications
Justin F.X. Ainscough; Mark J. Drinkhill; Alicia Sedo; Neil A. Turner; David A. Brooke; Anthony J. Balmforth; Stephen G. Ball. (2008). Angiotensin II type-1 receptor activation in the adult heart causes blood pressure-independent hypertrophy and cardiac dysfunction. Cardiovascular Research; doi: 10.1093/cvr/cvn230
Comparative Physiology of Purinergic Signalling

ATP is an ancient and fundamentally important biological molecule involved in both intracellular and extracellular activities. P2X ionotropic receptors for ATP have been cloned and characterised in mammals, where they play a central physiological role in processes including breathing, blood flow, taste, pain and inflammatory responses. Our research focuses on the comparative physiology of P2X receptors in simple organisms, like amoeba, in an effort to inform us about the cellular roles P2X receptors play in humans.

Comparative Physiology

Since the cloning of the first P2X receptors in 1994 our knowledge of this receptor class has been mainly restricted to vertebrates, were they can be found on central and peripheral nerves, muscular, glandular and inflammatory cells. We have previously demonstrated the existence of a P2X receptor in the amoeba Dictyostelium discoideum, a highly genetically amenable model organism that displays many animal cell traits (chemotaxis, phagocytosis, cytokinesis). The amoeba receptor is exclusively intracellular, localised to the contractile vacuole (a water pumping organelle). Knockout of the P2X receptor gene leads to an inability of cells to control their volume in hypotonic conditions, which lead to subsequent swelling (Figure 1), due to an impairment of the contractile vacuole. This was the first demonstration of a physiological role for an intracellular P2X receptor which was published in *Nature*. In the laboratory we are combining powerful techniques such as forward and reverse genetics, targeted biosensors, electrophysiology and confocal microscopy to study how a P2X receptor can control the function of an intracellular vacuole. Using this model we hope to make progress in our understanding of the roles P2X receptors resident in mammalian vacuoles (e.g. lysosomes, endosomes) may play.

Molecular Operation

In addition to amoeba, we have recently identified P2X receptors in several other single-celled organisms including algae (Figure 2). Without a crystal structure for a P2X receptor we have been restricted to looking at the protein sequences in order to understand how the receptor works and where drugs and ATP bind. Although protein sequence similarities between vertebrate P2X receptors are high, P2X receptors of single-celled organisms share low sequence similarities with vertebrate receptors. We are currently using this information to examine how the conserved protein residues in single-celled organism P2X receptors are involved in receptor function.

Importantly the receptors from single-celled organisms are insensitive to drugs that block human receptors. We are using molecular techniques to try and add blocking drug sensitivity back to several primitive receptors in order to better understand where drugs and ATP binds. We hope that this will lead to the development of better analgesic and anti-inflammatory therapies in man.

Funding:

BBSRC 5 year David Phillips Fellowship

More information:

http://www.fbs.leeds.ac.uk/staff/profile.php?tag=Fountain_S

Representative publications


Modelling the Link between Cardiac Structure and Cardiac Function

I am exploring the role of local myocardial structure in cardiac excitation and arrhythmia. The arrangement of the ventricular myocytes is controversial. In a leading model myocytes are arranged as regularly helically coursing fibres running through sheets. Structural studies by us and others show that sheets belong to two populations (of positive or negative orientation), have a complex distribution, vary in form between individuals and have localised regions of sudden orientation change. Ventricular electrophysiological propagation is significantly influenced by both fibre orientation and local sheet structure, and these and other heterogeneities are believed to play a role in the success or failure of defibrillation.

Detailed understanding of normal and deranged cardiac excitation requires the integration of knowledge of individual myocyte electrophysiology, cell interconnectivity, the 3D structural arrangement of myocytes and of the Purkinje system. I will test the hypothesis that differences in sheet structure, explicitly (i) regionally specific variations, (ii) inter-individual variations and (iii) structural change with the development of cardiomyopathy, will have a substantial impact on wave propagation and play a significant role in the development of arrhythmia. This will be achieved by building a comprehensive 3D virtual model of detailed cardiac structure and electrophysiology from experimental studies.

I will acquire structural and functional data from experimental studies of selected regions of the normal rabbit myocardium, at high spatial resolution and this will be extended to the whole left ventricle. These data will be built into an integrative structural computational model (Virtual Tissue). Electrophysiological propagation will be simulated, based upon experimental recordings and using the Virtual Tissue. Structural changes in the diseased myocardium will be incorporated by manipulation of the normal model, based on published rabbit studies and from our exploration of an available model of rabbit cardiomyopathy.

This will be supplemented with studies of post mortem canine tissue (from normal and cardiomyopathic hearts) which will allow the exploration of interspecies differences in health and disease.

Structure will be analysed using both DT-MRI and optical mapping. Optical mapping will be by multi-slice slide digitisation with digital reconstruction and by extended tissue confocal microscopy (of an entire rabbit heart).

The distribution of gap junctions and ion channels (as a marker of myocyte sub-type) will be mapped using immunohistochemistry and in situ hybridisation. These data will be complemented by recording the monophasic action potential and optical recording using voltage sensitive dyes (Fig. 2).

When the multi-layered and detailed virtual tissue has been constructed it will be used for the simulation of normal and abnormal electrical propagation. We will explore the roles of the anatomic distribution of fibres, sheets, gap junctions and cell types in electrical propagation. Electrophysiology recording will be used to refine the model, and the model will be used to redirect the recording studies.

The outputs will be i) detailed structural data, ii) a structural and simulation model, and iii) the knowledge from electrophysiological recording and simulation. Specifically, the hypotheses above will be tested by quantitative comparison of propagation in selected structural regions within and between hearts. Modelling will be used to explore the underlying mechanism of the quantified differences. This will add to the scientific understanding of the mechanisms of arrhythmia which will, in turn, facilitate development of therapies. Specifically the results may find application in clinical defibrillation studies.

Funded by: MRC

Collaborators: Dr Olivier Bernus, Dr Alan Benson, Professor Arun Holden, University of Leeds. Professor Mark Boyett, University of Manchester. Professor Bruce Small (Bioengineering Institute, University of Auckland, New Zealand.

More information: http://www.cardiovascular.leeds.ac.uk/staff/Gilbert_SH/
Cardiovascular Magnetic Resonance (CMR) Imaging

My primary area of interest is the role of CMR in patients with ischaemic heart disease. In particular, this includes the development and clinical application of comprehensive CMR protocols to assess left ventricular function, myocardial perfusion, tissue viability and coronary artery anatomy. We have applied these protocols to patients with both stable and unstable coronary artery disease. Of note, we have demonstrated both the safety and diagnostic accuracy of CMR imaging in acute coronary syndromes, including acute ST elevation myocardial infarction. Current major projects include:

1. Assessment of the diagnostic accuracy of CMR vs. SPECT, in a large patient cohort, with x-ray angiography as the reference standard, for the non-invasive detection of IHD. This includes a health economic evaluation of CMR and assessment of prognosis (Figure 1).
2. CMR assessment of myocardial tissue oedema, and the effect of potent systemic inflammatory agents at reducing myocardial damage and limiting ventricular dysfunction in patients with NSTEMI (Figure 2).
3. Evaluation of the value of CMR imaging to predict the potential for improvement in LV function after percutaneous coronary intervention to occluded coronary arteries (Figure 3).

Representative publications


Funding:
British Heart Foundation, NHS R&D, MRC, Heart Research UK

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Greenwood_J/ or www.cmr.leeds.ac.uk
Cardiac, Arterial & Molecular Solutions (CAMS) - Research Net

This regional network (Figure 1) works to discover, develop and deploy effective strategies to:
Identify and understand the mechanism of coronary artery disease
Prevent premature coronary artery disease (Figure 2)
Leeds collaborates closely with 20 surrounding Primary and Secondary Care NHS Trusts. This network will focus increasingly on methods for accurate patient profiling for diagnosis, prognosis and choice of treatment. It employs randomised trials and genetic/clinical epidemiology approaches.

In 1999 the Leicester and Yorkshire Family Heart Studies united to form a national BHF Family Heart Study that sought to identify and recruit 2,000 pairs of siblings affected by premature coronary artery disease. Furthermore this BHF Programme Grant funded a genome-wide linkage study. In parallel two other related collections took place (i) the ADLIB Project funded by the Medical Research Council (ii) the GRACE study funded through multiple grants. DNA from BHF FHS is stored at Leeds and Leicester Universities whereas the MRC and GRACE collections have been transferred for storage at the UK DNA Banking facility at Manchester University. From here the DNA from a total of 2,400 unrelated cases has been distributed to other sites as part of (i) the EU funded BLOODOMICS programme (ii) the Wellcome Trust Case Control Consortium and (iii) the EU funded CARDIOGENICS Programme. Most recently we have published in Nature and CARDIOGENICS Programme Most recently we have published in Nature and CARDIOGENICS Programme. The results of two large genome-wide association studies as part of the WTCCC and CARDIOGENICS programmes and performed additional revalidation studies of the key finding. Also we have initiated a complimentary “candidate gene” study of 50,000 single nucleotide polymorphisms in 1,500 UK cases and 1,500 UK controls (funded through Programme).

This work is being conducted using the Illumina ‘IBC chip’ which will allow us to fill important gaps in the earlier genome-wide scans (Figure 4). The SPACE ROCKET (Secondary Prevention of Acute Coronary Events Reduction of Cholesterol to Key European Targets) trial has been designed to assess the relative efficacy of two different statins, simvastatin 40mg vs. rosuvastatin 10mg. In addition to assessing efficacy the trial has been designed in a way to assess the tolerability of each agent. Although in large trials there is a clear cholesterol reduction from the usage of statins, in clinical practice there is a large inter-patient variability in response to cholesterol-lowering treatment. Within a number of trials between 25% and 30% of patients were intolerant of statin therapy. Consequently we have recruited and consented 675 patients into a genetic sub-study to evaluate the genetic modulators of inter-individual variation in response to statins. To date we have been focussing on common variants in the CYP450 3A5, 2C9 and 2C19 genes and are keen to extend our studies to include other genes that regulate the lipid metabolism pathways.

Funding:
Wellcome Trust, British Heart Foundation
AstraZeneca, Leeds Teaching Hospitals

Collaborators:
http://www.leeds.ac.uk/light/research/dept/cams-net/index.html

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Hall_AS/
Heart function in health and disease

My research interests lie in understanding the mechanisms of normal excitation-contraction coupling in the heart, how these processes are regulated and how a variety of 'disease states' (hypertrophy, sepsis, etc) and volatile general anaesthetics affect the strength of contraction of the heart. High blood pressure or 'hypertension' affects 10 million people in the UK (http://en.wikipedia.org/wiki/Hypertension). In hypertensive patients the heart has to work harder to pump blood around the body and this causes the walls of the heart to thicken (hypertrophy). Eventually hypertrophy can lead to heart failure and associated with this progression are changes at the cellular level in the way heart cells contract. We have been studying the mechanisms associated with altered contraction and calcium regulation in normal and hypertrophied heart cells (e.g. ref 3), in collaboration with Dr Ed White’s group we also compare ‘bad’ hypertrophy (above) with ‘good’ hypertrophy which occurs in athletes involved in endurance training (e.g. ref 4). We aim to understand why bad hypertrophy leads to heart failure whereas good hypertrophy does not. Sepsis (http://en.wikipedia.org/wiki/sepsis) is a potentially life-threatening condition associated with the release of inflammatory cytokines like tumour necrosis factor (TNF), these cytokines have direct inhibitory effects on the heart and contribute to cardiovascular complications. We have shown that combinations of TNF and interleukin-6 (IL-6) dramatically increase the leakiness of the internal store of calcium so that it cannot contribute properly during the heart beat. In Figure 2 the increased number of bright spots ('sparks') compared to Figure 1 represents increased leak of calcium from the store induced by these cytokines.

During surgery, volatile general anaesthetics (like halothane and sevoflurane http://en.wikipedia.org/wiki/Halothane) are routinely used to induce and maintain anaesthesia however, these agents have unwanted side effects on the heart. We have published more than a dozen papers since 1999 (e.g. ref 1) to further our understanding of how volatile anaesthetics affect the heart. Figure 3 shows the contraction of a single heart cell- halothane (top) initially increases then decreases whereas sevoflurane (middle) has the opposite effect. Mixing the two together (bottom) greatly reduced the impact on contraction.

Funding:
The British Heart Foundation, Wellcome Trust, Royal Society, Medical Research Council and the British Journal of Anaesthesia.

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Harrison_SM/

Representative publications


Arun Holden  
BA (Oxford, UK)  
PhD (Alberta, Canada) has been at Leeds since 1971, and is currently Professor of Computational Biology, and Deputy Director, centre for Nonlinear Studies, and is an editor of several nonlinear science journals and two book series on Nonlinear Science.  
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Computational Biology

(a) The computational Biology laboratory constructs detailed computer models of muscular organs - the beating heart, and the pregnant uterus - that are based on data from membrane, cell and tissue experiments, and from clinical data. These models are validated by their prediction of normal organ behaviour, and abnormal behaviours seen in disease. They are applied to dissect, in space and time, physiological and pathological mechanism, to prescreen drugs, and to contribute to the drug design and discovery process, and the design of physical interventions.

(b) Most of our research has been in the construction of cardiac virtual tissues, and these are now being applied to biomedical problems. Application areas include the normal pacemaking of the heart and its pharmacological control; the genetic engineering of pacemaking activity in the ventricles, as an alternative to implanted electronic pacemakers; the initiation and control of re-entrant arrhythmias in the atria and ventricles; the effects of drugs on propagation phenomena within the heart; and the effects of electrical and very large magnetic fields on the behaviour of the in situ heart. The same methodology, of developing and applying virtual tissues, is being applied to model uterine activity and possible mechanisms in premature and normal labour.

(c) An important new development has been the extraction of structural data, (geometry, cell orientation) from diffusion tensor magnetic imaging of tissues; this allows the reconstruction of a 3-D detailed digital map of an organ in a few days, rather than the months-years necessary for histological reconstruction.

More information:  
http://www.cardiovascular.leeds.ac.uk/staf/f/Holden/

Representative publications


Cardiac adaptation, rhythms and arrhythmias

My group’s research is directed towards understanding how the heart adapts to changing stresses to ensure sufficient cardiac output. Of particular interest are the stresses of exercise, cardiac damage and aging. Failure of the heart to adapt leads to cardiac insufficiency whereas undesirable adaptations cause increased susceptibility to arrhythmias and sudden death. By studying cardiac function at the global, cellular and sub-cellular levels we hope to develop an understanding of how intrinsic cardiac responses are controlled and may be manipulated.

One aspect of our research is directed at the initiation of heart beat. What makes the heart beat spontaneously and how is the beating rate regulated? This is a controversial topic. By measuring cardiac electrical activity in the presence of a variety of pharmacological modulators of intracellular calcium and with accompanying direct measurement of intracellular calcium using fluorescent probes (see Figure 1) we have discovered that calcium regulation is highly heterogeneous in the dominant cardiac pacemaker, the sinoatrial node. The work gives insight into the actions of catecholamines such as adrenaline and the generation of abnormal pacemaking.

An increasingly important aspect of cardiac physiology is the effect of aging on cardiac muscle performance. The aged heart is more susceptible to arrhythmias, shows reduced capacity for adaptation to common stresses such as exercise, and shows reduced tolerance to damaging insults such as a myocardial infarction. Research performed in conjunction with Dr Sandra Jones has begun to identify factors placing the aging heart at increased risk and limiting its adaptive capability. Identification of changes in ion-channel expression and intracellular signalling has already identified potential mechanisms underlying an increased propensity for atrial arrhythmias in the elderly and we are building on this work.

Funding
Strategic Promotion of Ageing Research Capacity, a BBSRC/EPSRC joint venture

Overseas Collaborators
Haruo Honjo (Japan) and Scott Powers (USA)

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Lancaster_M/

Representative publications


BHF Research Unit: Role of genetic variation in cardiovascular disease

Coronary artery disease (CAD) and its most important complication, myocardial infarction (MI) are the leading cause of premature death in the Western World. CAD has a substantial genetic basis and the major part of the work undertaken by our grouping is to investigate the role of genetic variation in the pathology of disease.

Candidate Gene Studies
The role of genetic variation in candidate genes involved in a number of cardiac pathologies including heart failure, left ventricular hypertrophy as well as CAD and MI are being investigated. These studies allow us to correlate clinical parameters of disease with allelic variation.

Genome Wide Studies: British Heart Foundation Family Heart Study
We investigated the genetic determinants of premature CAD by performing genome wide linkage analysis of more than 2000 sib-pairs using 416 microsatellite markers. We observed suggestive linkage for both CAD and MI to a region on chromosome 2. This work was completed in 2005 and was performed in conjunction with the University of Leicester. Subjects recruited for the study were also included in the Wellcome Trust Case Control Consortium Study (2007) which highlighted a region on chromosome 9 associated with premature CAD

Genetic variation in the control of sympathetic regulation
We are currently investigating the role of genetic variation on the alpha 2 adrenergic receptors in the control of central sympathetic activity. This work is being undertaken in conjunction with the microneurography laboratory at St. James’s University Hospital which has enabled us to quantify sympathetic drive in both volunteers and in patients with hypertension.

Funding:
British Heart Foundation (BHF)

Collaborators:
Stephen Ball
David Mary
Anthony Balmforth
Alistair Hall

Representative publications


Myosins, muscle and disease

Myosin and actin are essential for heart and skeletal muscle contraction, and for intracellular movement in non-muscle cells. In heart and skeletal muscle these proteins form separate filaments, in a repeating structure called the sarcomere (Figure 1). In non-muscle cells, the arrangement of actin filaments and myosins is more disorganized. We use cell culture, molecular genetics and microscopy to understand how muscle contracts, how filaments and sarcomeres assemble, how mutations in sarcomeric proteins cause muscle disease and how non-muscle myosins operate.

Mutations in muscle proteins lead to early death from heart failure. We showed that cultured muscle cells expressing myosin mutations contracted faster than normal. We are now exploring other myosin mutations, as well as mutations in other sarcomeric proteins that can affect sarcomere assembly and result in diseases such as nemaline myopathy (with John Sparrow, York). One of these proteins is titin, a muscle protein that controls sarcomere organization. We were the first to find that the titin’s kinase and M-line region is essential for sarcomere assembly. We are now engineering single-amino-acid changes into the kinase (with Andrew Smith, Edinburgh and Mathias Gautel, KCL) in embryonic stem cells, which can grow into heart muscle, to determine how this region controls sarcomere assembly.

Myosin 10, found in non-muscle cells, does not form filaments and appears to transport intracellular components to the outer cell membrane (Figure 2). We used total internal reflection fluorescence microscopy (tIRFM) to show which region of myosin 10 targets it to the cell membrane. We were also the first to show that this myosin contains a structure to help it take bigger steps on interaction with actin.

Overseas collaborators:
Angélica Keller (Paris), Jim Sellers (USA), Kathy North (Sydney)

Funding:
Wellcome Trust, British Heart Foundation, BBSRC, British Council

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Peckham_M/

Representative publications


Knight, PJ, Thirumurugan, K, Xu, Y et al. (2005) The predicted coiled-coil domain of myosin 10 forms a novel elongated domain that lengthens the head. Journal of Biological Chemistry 80: 34702–34708


Figure 1: actin filaments (red), myosin filaments (green) and the nucleus (blue) in a heart muscle cell. Arrow, one sarcomere.

Figure 2: Fluorescently tagged myosin 10 in living cells, imaged using TIRFM. The bright red spots show that most myosin 10 is at the cell periphery. (in collaboration with Justin Molloy and Gregory Mashanov, NIMR)
Remodelling of Cellular Functions by Hypoxia in Health and Disease

Research is centred around understanding how we sense low levels of oxygen (hypoxia), and how hypoxia alters various cellular functions. Oxygen sensing involves various diverse mechanisms, and we have demonstrated two key pathways: (i) O2 dependent generation of carbon monoxide, which acts as a secondary signalling molecule (Fig. 1) and (ii) activation of AMP-activated protein kinase, which phosphorylates key target proteins to transducer hypoxic signals (Fig. 2). In both cases, ion channels and Ca2+ homeostatic mechanisms are key targets of oxygen sensing processes.

Sustained hypoxia alters protein expression and can lead to cell death. It has been implicated in the development of neurodegenerative diseases such as Alzheimer’s disease. We have shown hypoxia in vitro increases production of the key toxic peptide of Alzheimer’s, amyloid β peptide. This has dramatic, deleterious effects on ion channel functional expression and Ca2+ homeostasis (Fig. 3). We are currently probing the mechanisms underlying hypoxic increases in amyloid production.

Additional current projects include studies of the effects of hypoxia on Ca2+ homeostasis in human endothelial and vascular smooth muscle cells, as well as effects of “gasotransmitters” (nitric oxide, carbon monoxide, hydrogen sulphide) in various tissue systems including the central nervous and cardiovascular systems. All experiments employ patch-clamp electrophysiology, Ca2+ imaging and supportive molecular biological techniques to identify, manipulate and eliminate proteins of interest.

Funding:
Wellcome Trust, MRC, British Heart Foundation, Alzheimer’s Research Trust

Collaborators:
AM Evans (Edinburgh)
DG Hardie (Dundee)
NS Chandel (Chicago)
CN Wyatt (Dayton)

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Peers_C/

Representative publications


Advanced Imaging of Myocardial Ischaemia

My work in the Cardiac Magnetic Resonance (CMR) Research group is focused on the development and clinical application of new and improved methods for the assessment of myocardial ischaemia and heart failure. CMR is the most exciting non-invasive imaging modality for the in vivo study of cardiac physiology and pathophysiology and provides data with high resolution without exposure to ionising radiation or potentially harmful intervention.

Comprehensive CMR imaging

We have developed a comprehensive CMR protocol for multi-parametric assessment of coronary artery disease. This allows the combined evaluation of myocardial perfusion, contractile function, myocardial viability and coronary artery anatomy. Facilitated by our location in a large tertiary cardiology centre, we have applied this protocol in clinical studies of chronic stable coronary artery disease and acute coronary syndromes. One of our major current projects is the CEMARC study, which will be the largest prospective evaluation of CMR for the detection of IHD compared with current diagnostic strategies (funded by a BHF programme grant). These studies were carried out at 1.5 and 3 Tesla. At such detail, an assessment of transmural myocardial perfusion, i.e. its distribution between the endocardial and epicardial layers, becomes feasible. We are now studying these transmural gradients against invasive measurements of ischaemia.

High spatial resolution CMR perfusion

In collaboration with the ETH and University of Zurich I have developed methods that permit a highly detailed assessment of myocardial perfusion at a spatial resolution close to 1mm (funded by a Wellcome Trust fellowship). These studies were carried out at 1.5 and 3 Tesla. At such detail, an assessment of transmural myocardial perfusion, i.e. its distribution between the endocardial and epicardial layers, becomes feasible. We are now studying these transmural gradients against invasive measurements of ischaemia.

Figure 1. High spatial resolution myocardial perfusion MR image showing ischaemia in the infero-lateral left ventricular myocardium (arrows). The transmural distribution of ischaemia with sparing of the epicardium can be clearly appreciated.

Non-ischaemic cardiomyopathy

We are increasingly interested in myocardial perfusion and contractile abnormalities associated with small vessel disease. The high-resolution perfusion methods we have developed are being employed to determine myocardial flow redistribution in patients with diabetes mellitus. Another study assesses the cardiovascular effects of chemotherapy for breast cancer (both funded by the Leeds Charitable Foundation).
Molecular and Cellular Biology of Vascular and Myocardial Remodelling

My group has two major research interests - the cellular biology of intimal hyperplasia (in human saphenous vein bypass graft stenosis), and the study of human cardiac fibroblast function in relation to the progression of heart failure. The strength of our research is the use of the exact human tissues and cells involved in cardiovascular pathologies – vascular endothelial and smooth muscle cells and cardiac fibroblasts. “Adverse remodelling” is a common feature of these pathologies, and is characterised by excessive cell proliferation, migration and disrupted extracellular matrix metabolism. Increased activity of metalloproteinases (MMPs) plays a pivotal role in extracellular matrix degradation, permitting cell proliferation and invasion that contribute to the remodelling process. In particular, MMP-2 and MMP-9 are basement membrane-degrading gelatinases that appear to play an important role in the development of both graft stenosis and heart failure.

STATINS - We are especially interested in the commonly prescribed cholesterol-lowering drugs statins and their effects on vascular and cardiac remodelling. We have shown that statins have beneficial cellular effects that are independent of their lipid-lowering properties. Our research has revealed that simvastatin reduces neointimal thickening in organ cultures of human saphenous vein by inhibiting smooth muscle cell (SMC) proliferation and migration. We have focussed on determining the intracellular mechanisms that underlie the anti-invasive properties of statins in cultured human SMC, with particular emphasis on the regulation of MMP-9. Similarly we have demonstrated comparable beneficial properties of statins on human heart fibroblasts – effects that help to explain the therapeutic benefits of these drugs to reduce the progression of heart failure.

Our work clearly indicates that statins have far greater benefits on human cardiovascular cells than can be attributed to cholesterol-lowering alone.

DIABETES - Cardiovascular disease in patients with diabetes is a serious and escalating problem worldwide; these patients are at significantly higher risk of cardiovascular disease than the non-diabetic population. Insulin therapy is used to treat hyperglycaemia in diabetic patients, yet even when blood glucose is well controlled, these patients still suffer cardiovascular complications, such as restenosis after coronary artery bypass surgery. Our present studies aim to elucidate the cellular and molecular mechanisms that contribute to increased cardiovascular risk in diabetes. This is facilitated by our ability to compare cells and tissues from patients with and without diabetes. Increasing our understanding of the aetiology of cardiovascular disease in the diabetic population may assist in designing strategies to prevent and/or treat this vulnerable population.

Funding:
British Heart Foundation, Heart Research UK

Collaborators:
UK – Professor David Beech, University of Leeds.
Professor Chris Peers, University of Leeds. International - Professor Marlys Koschinsky, University of Windsor, Ontario, Canada.

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Porter_K

Representative publications


Exercise bioenergetics in health and disease

My research programme focuses on the process involved in oxygen transport to, and utilisation in, skeletal muscles during exercise. These processes are important because the ability to sustain muscular exercise is highly dependent on the ability to synthesize energy using mechanisms that consume oxygen. Furthermore, because nearly all conditions of physical activity are non-steady-state (i.e., energy demands are continually changing), I am particularly interested in how the dynamics of the cardiovascular and muscular systems interact to allow exercise to be maintained. A basic understanding of the energy systems that contribute to energy production (termed bioenergetics) during exercise will help us provide ameliorative therapies for populations where these processes are impaired. These systems integrate to transport oxygen from the atmosphere to where it is utilised by the muscle mitochondria. In addition, my research with Dr Ellen Breen and Dr Miriam Scadeng (University of California, San Diego) has combined magnetic resonance imaging and molecular biology techniques to investigate the mechanisms that cause lung disease (Figure 3), and how these are involved in limiting the ability to sustain muscular exercise.

Using magnetic resonance (MR) spectroscopy (in collaboration with Dr Graham Kemp, University of Liverpool) and magnetic resonance imaging (in collaboration with Professor Yoshiyuki Fukuba, Hiroshima Prefectural University, Japan) in humans we are able to ‘look inside’ skeletal muscle during exercise and investigate the biochemical pathways contributing to the energy provision within the recruited musculature (Figure 2). Ours is the only laboratory in the world to have combined dynamic pulmonary and intramuscular measurements in humans to show how the kinetics of these systems integrate to transport oxygen from the atmosphere to where it is used by the muscle mitochondria. In addition, my research with Dr Ellen Breen and Dr Miriam Scadeng (University of California, San Diego) has combined magnetic resonance imaging and molecular biology techniques to investigate the mechanisms that cause lung disease (Figure 3), and how these are involved in limiting the ability to sustain muscular exercise.

In the Human Physiology laboratory in Leeds (and in collaboration with Dr John Kowalchuk, University of Western Ontario, Canada) I use state-of-the-art cardiopulmonary exercise testing (Figure 1) to determine cardiovascular and pulmonary dynamics in response to known work rates.

Figure 1: Cardiopulmonary exercise testing in the Human Physiology laboratory.

Figure 2: Spectroscopic and anatomic magnetic resonance analyses of human quadriceps before, during and after high-intensity dynamic exercise.

Figure 3: 3D computer models of murine lung structures from 80μm isotropic magnetic resonance images at 7T. The models show the large pulmonary airways (yellow) and small pulmonary structures (cyan) as well as the heart and aorta (red) and oesophagus (blue).

Funding: The Wellcome Trust, National Institutes of Health (USA), Worldwide Universities Network, American Physiological Society

More information: http://www.cardiovascular.leeds.ac.uk/staff/Rossiter_H/index.htm

Representative publications


Potassium channels in health and disease

Voltage-gated ion channels control transmission of nerve impulses, heartbeat, muscle contraction and hormone secretion. Defects in function can cause disease, including epilepsy, cardiac arrhythmia, myotonia and periodic paralysis, so these channels are important drug targets. All such channels have a gated pore with four voltage-sensing domains attached. The sensors detect voltage changes across the cell membrane and signal to pore gates to open or close in response. Our goal is to elucidate the structural basis for voltage sensing and the consequent motion of pore gates. The three-dimensional structures of voltage-gated ion channels have recently been determined (Figure 1). To facilitate these studies we study three channel proteins: the prototypical Shaker potassium channel, the archaeabacterial KvaP and the HeRg potassium channel. In addition, we also study ATP-sensitive potassium channels which are sensors of blood glucose and play a central role in insulin secretion and maintenance of blood glucose levels. Loss-of-function mutations in the genes encoding this channel cause the rare genetic disease congenital hyperinsulinism, characterized by unregulated secretion of insulin and severe hypoglycaemia. Gain-of-function mutations cause neonatal diabetes, with severe hyperglycaemia. Mutations causing type-2 diabetes also appear to be associated with the genes encoding these channels. Our aim is to elucidate the basis of how genetic mutations affect these channels, and understand the basis for the disorders of insulin secretion. We are also screening for new drugs that alter the trafficking of these channels, and may have therapeutic potential (Figure 2).

Funding:
Wellcome Trust, MRC, BHF, GlaxoSmithKline

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Sivaprasadarao/

Representative publications


Most of my work addresses the role of the sarcoplasmic reticulum (SR) Ca2+ channel (ryanodine receptor, RyR) in cardiac and skeletal muscle. In cardiac and skeletal muscle, electrical excitation of the surface membrane causes Ca2+ release from the SR and contraction of myofilaments. We study SR Ca2+ release in normal cells and aberrant Ca2+ release in disease (ischaemia, inherited cardiomyopathies). Our recent work on cardiac muscle has addressed the role of the t-tubules in excitation–contraction coupling, changes in SR Ca2+ regulation associated with ischaemia or anoxia (e.g. ATP depletion) and the cardioprotective effects of volatile anaesthetics. Recently we described long-lasting Ca2+ release events that may be involved in regulation of gene transcription or expression. In a collaborative project (with Noriaki Ikemoto and Graham Lamb) we are using peptides to induce and study abnormal RyR2 gating associated with inherited arrhythmias. This ‘peptide probe’ technique is based on the hypothesis that in normal RyR2 channels interaction between the N-terminal and central domains stabilizes the channel (Figure 1).

Mutations in these regions can induce abnormal Ca2+ release and consequent arrhythmias. Our work on skeletal muscle addresses the development of fatigue and malignant hyperthermia, an inherited condition associated with potentially fatal increases in core body temperature, triggered by exposure to volatile anaesthetics (Figure 2). The abnormality is known to be caused by mutations in RyR1, which result in sustained Ca2+ release and contraction during anaesthesia. Working with clinicians and geneticists (St James’s Hospital, Leeds) we have shown that reduced Mg2+ inhibition of RyR1 is a common feature of many channel mutations and may explain the abnormal response to anaesthetics. Ongoing work involves characterization of novel RyR1 mutations and development of non-invasive DNA based screening.

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Postdoctoral research at Glasgow
Lecturer (1996-2000)
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Ryanodine receptor function in skeletal and cardiac muscle

Funding:
Wellcome Trust, British Heart Foundation, Department of Health

Overseas collaborators:
Noriaki Ikemoto, Graham Lamb (Australia)

More information:
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Representative publications


Figure 1: Proposed interaction between the N-terminal and central RyR2 domains.

Figure 2: Image sequence showing a propagated Ca2+ wave induced by halothane in a mechanically skinned human skeletal muscle fibre from a patient with malignant hyperthermia.
Structure, function and regulation of proteases

Proteinases play a key role in many aspects of cell regulation—from fertilization and embryogenesis to cell death, the main focus of our research is understanding the functions of critical proteinase targets in brain, the cardiovascular system and reproductive tissue. A primary focus involves the neprilysin (neP) family of zinc metalloproteinases, originally discovered by us and widely distributed in nature. We use functional genomics to understand the roles of neP homologues in vertebrates and invertebrates. We have projects in the areas of heart disease, Alzheimer’s disease and prostate cancer. We have cloned and characterized a novel homologue (ace2) of the blood pressure-regulating enzyme, angiotensin-converting enzyme (ace). Ace2 is now known to have key roles in regulation of heart and lung function and is also the SARS virus receptor. We are exploring aspects of its structure (Figure 1) and physiological roles and whether ace2 might constitute a novel therapeutic target, as well as possible novel functions of ace itself.

We are also investigating the proteolytic events involved in the production and removal of the β-amyloid peptide, characteristic of the amyloid plaques of Alzheimer’s disease (Figure 2). Key aspects of amyloid formation currently being explored by us are its biological regulation and subcellular location, particularly the roles of membrane ‘lipid rafts’ and cellular cholesterol levels in these processes. NeP and its homologue ece play key roles in amyloid removal and we are studying processes such as hypoxia and oxidative stress in modulation of these events.

Funding:
BBSRC, BHF, EU (INTAS), MRC, Prostate Cancer Research Foundation, Wellcome Trust, Yorkshire Cancer Research

More information:
http://www.cardiovascular.leeds.ac.uk/staff/Turner_AJ/

Representative publications


Intracellular Mechanisms Regulating Adverse Cardiovascular Remodelling

The general aim of my research is to understand key intracellular signalling mechanisms that regulate adverse remodelling of the cardiovascular system, using cultured human cells from the heart and vasculature as model systems. The main areas of my research are focussed on the cardiac fibroblast, an important (though often overlooked) cell type that maintains the structural integrity of the heart. Importantly, following a myocardial infarction (MI), cardiac fibroblasts undergo a phenotypic change to become myofibroblasts, activated cells that play a key role in post-MI scar formation and remodelling. Some of the key functional responses of cardiac myofibroblasts include increased proliferation, migration, cytokine secretion and matrix protein synthesis and degradation, the latter being regulated by matrix metalloproteinases (MMPs). These functions of cardiac myofibroblasts are extremely important for post-MI healing. However, if these responses continue unchecked they can be detrimental by contributing to adverse myocardial remodelling and heart failure progression. Hence, studying the mechanisms underlying key functions of cardiac (myo)fibroblasts, and developing therapeutic approaches to target them, is important.

Role of the p38 MAPK signalling pathway in regulation of human cardiac myofibroblasts.

The p38 mitogen-activated protein kinase (MAPK) signalling pathway appears to potentiate adverse myocardial remodelling. There are four known p38 MAPK subtypes (alpha, beta, gamma and delta) that exhibit cell- and tissue-specific expression and play differential roles in cellular functions. By identifying the specific stimuli that activate individual p38 MAPK subtypes, and determining the effects of p38 MAPK subtype inhibition on cardiac (myo)fibroblast function, a clearer understanding of the role of the p38 MAPK pathway in the myocardial remodelling process will be obtained.

Mechanism of β2-adrenergic receptor induced cardiac fibroblast proliferation.

β-adrenergic receptor antagonists (beta-blockers) can reduce myocardial remodelling and one mechanism by which they may act is through direct effects on cardiac fibroblast function. We have shown that adult human cardiac fibroblasts express the β2-adrenergic receptor (β2-AR) and that β2-AR stimulation increases fibroblast proliferation. We have proceeded to define the underlying mechanism and found that it involves β2-AR-induced secretion of autocrine growth factors that stimulate proliferation via an endothelin-1 dependent mechanism.

Intracellular mechanisms by which statins modulate cardiovascular cell function.

We have demonstrated that cholesterol-lowering drugs (statins) have favourable effects on human cardiac fibroblast and smooth muscle cell function that may explain some of the cholesterol-independent benefits of these drugs. Statins reduce cardiac fibroblast proliferation, migration and MMP expression by inhibiting intracellular membrane attachment of the small G-protein, RhoA. Statins have similar effects on human vascular smooth muscle cells, but the underlying mechanisms appear to be quite different.

Funding:
British Heart Foundation, Research Councils UK

More information:
http://www.leeds.ac.uk/medhealth/light/staff/turner_n.html

Representative publications


Mechanical stimulation of the heart

Acute mechanical stimulation (e.g. stretch) affects the contractility of cardiac muscle in situations such as exercise, when diastolic ventricular volume is increased. But stretch has also been implicated in the triggering of cardiac arrhythmias. Chronic stretch provokes cardiac hypertrophy. Thus stretch may be involved in the beneficial effects of regular exercise and the cause of heart attacks, depending upon the circumstances. My research group is interested in the cellular mechanisms that cause these varied effects. We have research collaborators in France and the UAE and the laboratory has welcomed researchers from Brazil, Canada, France, Japan, Poland and the UAE.

We can study the effects of acute stretch on single cardiac myocytes by attaching carbon fibres to the cell (Figure 1A) and recording the change in force (Figure 1B) or intracellular calcium (see Calaghan & White, 2004 J.Physiol. 559, 205-214) or electrophysiology (Belus & White, 2003). The triggers for hypertrophy in response e.g. to hypertension or to voluntary exercise are studied using functional approaches in conjunction with molecular biological techniques such as mRNA arrays and Western blotting.

We are also interested in the role components of the cytoskeleton such as microtubules (Figure 2, Calaghan et al, 2001) may play as transducers of mechanical stimuli. a recent interest is the role that caveolae, small invaginations on the surface of the myocytes might play in the signalling of stretch (Calaghan & White, 2006).

More information:
http://www.cardiovascular.leeds.ac.uk/staff/White_E/

Representative publications


Gene regulation in cardiovascular disease

My group is interested in understanding the mechanisms responsible for altered regulation of gene expression in cardiovascular disease. Our studies encompass both the heart and blood vessels and we focus mostly on a transcription factor whose dysfunction is important in several cardiovascular diseases such as cardiac hypertrophy and vascular proliferative diseases.

The transcription factor REST plays a pivotal role in regulating gene expression in the heart and blood vessels. We have shown that reduced function of REST is a driver of vascular smooth muscle proliferation and cardiac hypertrophy. We are currently investigating the role REST plays in the activation of cardiac fibroblasts and the contribution of REST dysfunction, as a consequence of diabetes, to cardiovascular disease.

REST is a nexus for complex gene regulatory networks combining a response to cell signalling, pathways with an epigenetic readout. Adapted by permission from Macmillan publishers Ltd from: Ooi L and Wood IC. Nature Reviews Genetics 8, 544-554. copyright (2007).