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Contents

Editorial

Happy New Year and Welcome to the January 2008 issue of *The* Bulletin!

We are pleased to bring you an insightful review of the therapeutic potential of preconditioning and postconditioning, written by Derek Yellon and colleagues at the Hatter Institute and Centre for Cardiology. We also include a mini-review, written by BSCR Prize winner Ian Sabir and colleagues on restitution curves and ventricular arrhythmogenesis. Congratulations, Ian, on an excellent study.

Chris Jackson dives straight in to his new role as BSCR Secretary, providing us with a highly entertaining first column. We wish Chris well in his new position and look forward to working with him.

The BSCR has continued to be active in organising scientific meetings and symposia and we include reports on two such meetings in this issue. Yvonne Alexander reports on the BSCR Symposium at last summer's BCS meeting on Vascular Calcification and Mike Curtis reports on proceedings at the BSCR Autumn meeting on 'The QT interval and drug-induced torsades de pointes'.

Fleur Moseley returns from the AHA meeting in Orlando and shares the highlights and her experiences with us - as well as an amusing photo of a brave committee member enjoying a terrifying rollercoaster ride.

Helen Maddock and Nicola Smart

Protecting the ischaemic diabetic heart

by Derek J Hausenloy, Christopher CT Smith and Derek M Yellon

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Introduction

Coronary heart disease (CHD) is the leading cause of death in the UK, accounting for over 100,000 deaths per year. Despite the timely application of reperfusion strategies such as thrombolysis and more recently primary percutaneous coronary intervention (PCI), the 30-day mortality following an acute myocardial infarction (AMI) remains significant at around 10%, paving the way for novel cardioprotective strategies to be explored.

In particular, the diabetic population are a patient group with the most to gain from such an approach, given the fact that diabetic patients are 2 to 3 times more likely to develop CHD (such that the presence of diabetes is considered to be a CHD risk-factor equivalent associated with a 10 year-risk of $\geq$ 20% for developing a coronary event), and that the mortality is increased twice-fold in diabetic patients experiencing an AMI. Two such cardioprotective strategies under intense pre-clinical investigation are ischaemic preconditioning and the more recently described ischaemic postconditioning. This article will provide a brief introduction to these cardioprotective phenomena and review the exciting possibility of harnessing their protective potential through the utilisation of antidiabetic agents which appear to exert non-hypoglycaemic cardioprotective benefits.

Ischaemic preconditioning and postconditioning

The term ischaemic preconditioning (IPC), which was first introduced in 1986 by Murry and colleagues (1), describes the reduction in myocardial infarct size observed in canine hearts subjected to four short bouts of myocardial ischaemia (see figure 1). The elucidation of the potential protective mechanism of this exciting and unexpected phenomenon, which appears to be both ubiquitous, protecting in every species tested, as well as non-organ specific as its protective potential can be applied to other organs such as the brain, intestine and muscle (reviewed in (2)), has generated great interest, resulting in the publication of nearly 4,000 studies. However, the potential of IPC has not yet been realised in the clinical arena of myocardial ischaemia-reperfusion, due in part to the limitation of having to intervene before the onset of the acute myocardial infarction, which is of course, unpredictable. This however, does not exclude its use in other clinical settings where the onset of myocardial ischaemia can be reliably anticipated such as in patients undergoing elective PCI, cardiac bypass surgery or in patients presenting with unstable angina.

Therefore, for those patients presenting with an AMI, an intervention which can be applied as an adjunct to the current reperfusion strategies of thrombolysis and primary PCI, would provide a far more attractive and amenable strategy of cardioprotection. In this regard, the phenomenon of ischaemic postconditioning (a term first introduced in 2003 (3)), which describes the reduction in myocardial infarct size obtained from interrupting the myocardial reperfusion phase with short bouts of myocardial ischaemia (see figure 1), has generated much excitement in the field of cardioprotection, as it offers an intervention which can be applied at the time of myocardial reperfusion in patients presenting with an AMI (reviewed in (4)).

Importantly, two small clinical studies have realised the cardioprotective potential of ischaemic postconditioning in the clinical arena, in patients undergoing primary PCI for an AMI (5;6). These studies demonstrated that interrupting myocardial reperfusion by applying several low pressure inflations/deflations of the coronary angioplasty balloon, in patients undergoing primary PCI, resulted in a 36% reduction in myocardial infarct size as measured by CK release, improved coronary blood flow, and facilitated ST segment resolution (5;6).

The mechanism through which repetitive bouts of non-lethal myocardial ischaemia, whether they be applied prior to the onset of the AMI (as in the case of IPC) or at the time of reperfusion (as with ischaemic postconditioning), actually reduce myocardial infarct size is unclear, although G-protein receptor activation with endogenous ligands (such as adenosine and bradykinin),

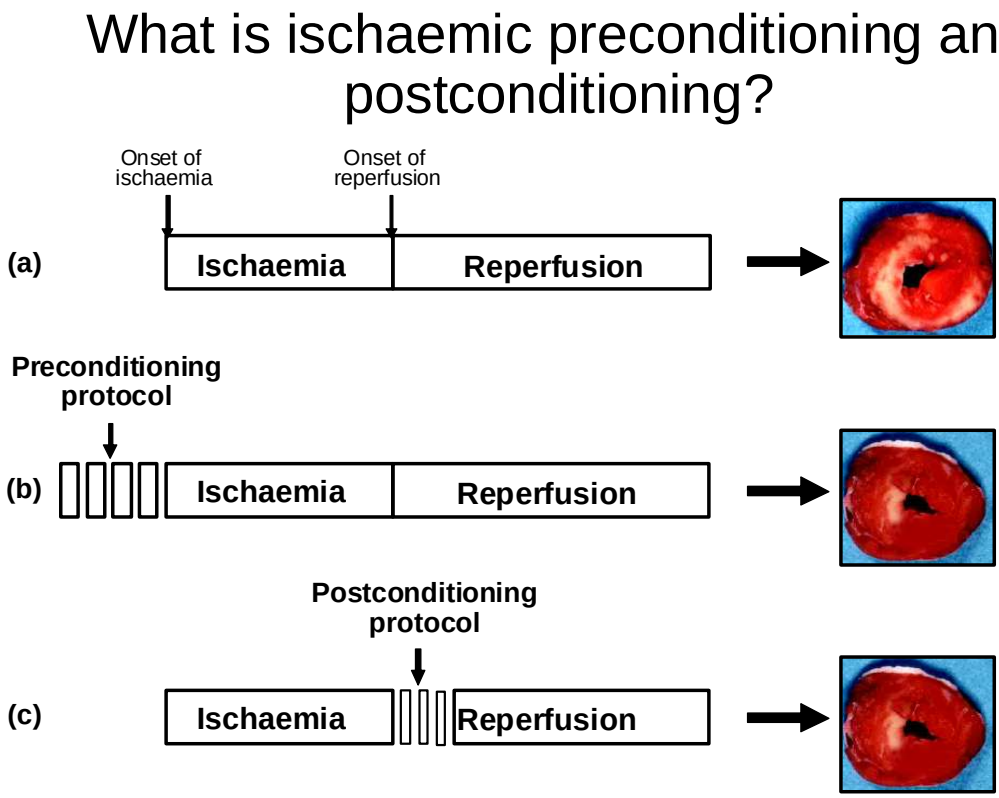

Figure 1. This figure demonstrates the myocardial infarct (represented by the white area in a section of a rabbit heart) produced by a standard period of myocardial ischaemia followed by an episode of myocardial reperfusion. Interestingly, the size of the myocardial infarct can be drastically reduced by either administering several bouts of short-lived myocardial ischaemia prior to the sustained episode of myocardial ischaemia (so-called ischaemic preconditioning [b]) or by interrupting myocardial reperfusion with several bouts of short-lived myocardial ischaemia (so-called ischaemic postconditioning [c]).

the activation of protein kinases (such as Akt, Erk1/2, and PKC), intracellular redox signalling and the inhibition of the mitochondrial permeability transition pore (mPTP, the opening of which is a critical mediator of cell death, reviewed in (7)) have all been implicated (see figure 2).

Whether the diabetic myocardium can be protected by the cardioprotective manoeuvres of ischaemic preconditioning or postconditioning is unclear. Studies from our laboratory and others suggest a defect in protein kinase signalling, specifically the PI3K-Akt kinase pathway in the diabetic heart (8), may contribute to the lack of protection in these settings, and that the protective effect may be restored by either increasing the intensity of the preconditioning or postconditioning stimulus (9) or by administering hypoglycaemic agents such as glimepiride (unpublished data from our laboratory) or rosiglitazone which may act to augment levels of the protein kinase, Akt (10).

It is interesting to note that by acting on the various components of the mechanistic pathway depicted in figure 2, certain anti-diabetic agents may act either to reproduce and mimic the cardioprotective effects of ischaemic preconditioning and postconditioning or conversely these anti-diabetic agents may actually interfere with protection in these settings (see figure 3).

The cardioprotective potential of antidiabetic agents

Insulin

Insulin was first proposed as a cardioprotective agent in the setting of an acute myocardial infarction, as part of a metabolic cocktail comprising glucose, insulin and potassium (GIK), by Sodi-Pallares in 1962 (11). Following several inconclusive studies in the 1960's and 1970's, the use of the GIK regimen re-emerged as a potential cardioprotective strategy following the

publication of a meta-analysis reporting a 21% significant reduction in mortality (12), and the DIGAMI clinical trial in which GIK therapy resulted in a 29% significant reduction in mortality (13) as well as the ECLA clinical trial which reported a 66% reduction in mortality in diabetic patients reperfused following an acute myocardial infarction (14). However, a subsequent large multi-centred randomised controlled clinical trial reported that a 24-hour infusion of GIK did not have any significant effect on morbidity or mortality in patients presenting with an acute ST-elevation MI (15).

Pre-clinical studies from our laboratory have reported that the administration of insulin at the immediate onset of myocardial reperfusion reduced myocardial infarct size in the isolated perfused rat heart, through the action of protein kinases such as Akt and p70S6K (16), and subsequent inhibition of mPTP opening (17). Of note and of potential relevance to the negative findings in the clinical CREATE-ECLA study (15), we found that if insulin was not given at the immediate onset of myocardial reperfusion, no protective effect was observed (16).

Sulphonylurea and nonsulphonylurea insulin secretagogues

Sulphonylureas (such as glibenclamide, gliclazide and glimepiride) as well as the newer nonsulphonylurea glinides (such as repaglinide and nateglinide) increase basal and post-prandial insulin secretion by closing the ATP-dependent potassium (K_{ATP}) channel in pancreatic B-cells. It is their antagonistic effect on K_{ATP} channels within the heart which accounts for their potential interference with the cardioprotective manoeuvres of ischaemic preconditioning and postconditioning, as the K_{ATP} channel, particular the mitochondrial form, is believed to play an important role in this setting. Preclinical studies have reported that the sulphonylurea glibenclamide, but interestingly not gliclazide (18), glipizide (19) or glimepiride (20), abrogated the protective effect induced by either ischaemic preconditioning (21) or postconditioning (22). This initial fear of sulphonylureas increasing cardiovascular mortality in diabetic patients (by potentially interfering with ischaemic preconditioning) was not borne out by the UKPDS trial (23). Further studies are required to investigate whether the glinides have any effects on cardioprotection in particular ischaemic preconditioning and postconditioning as they too act by closing the K_{ATP} channel.

Whether the α-glucosidase inhibitors such as acarbose exert a non-hypogylcaemic cardioprotective effect has not yet been examined in the preclinical or clinical setting.

Biguanides (Metformin)

In 1998 the UKPDS study demonstrated that metformin reduced the risk of MI in diabetic patients (23), in addition to exerting a cardioprotective effect in diabetic patients presenting with an acute coronary syndrome (24) or undergoing PCI (25). The mechanism of cardioprotection is unknown, although preliminary pre-clinical studies from our laboratory have found that metformin reduces myocardial infarct size through the activation of protein kinases such as Akt or Erk1/2 in a rat heart model of ischaemia-reperfusion injury (unpublished data from our laboratory). Furthermore this protection appears to be executed through an Akt-mediated inhibition of mitochondrial permeability transition pore opening which may in part explain the cardioprotective properties observed in clinical studies patients (23).

Thiazolidinediones

Thiazolidinediones such as pioglitazone and rosiglitazone are peroxisome proliferators-activated receptor gamma (PPAR-γ) agonists which enhance insulin sensitivity, increase peripheral glucose uptake and improve pancreatic B-cell function. Clinical studies have reported that the treatment of diabetic patients with thiazolidendiones exerts a cardioprotective effect as evidenced by a reduction in the risk of MI in diabetic patients presenting with an acute coronary syndrome (24) as well as diabetic patients with no prior history of MI (26). A recent randomized control trial reported that pioglitazone reduced the combined secondary end-point of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with diabetes (27). The actual mechanism of cardioprotection is unclear and has been attributed to the pleiotropic effects of this group of drugs. Preclinical studies have found that both pioglitazone (28) and rosiglitazone (29) reduce myocardial infarct size in animal models of ischaemia-reperfusion. We and others have found that this infarct-limiting effect is mediated through the activation of protein kinases such as Akt or Erk1/2 (10;30).

Glucagon-like peptide 1 and its analogues

Glucagon-like peptide 1 (GLP-1) is an incretin hormone produced by the intestinal L-cell in response

Cardioprotective antidiabetic agents

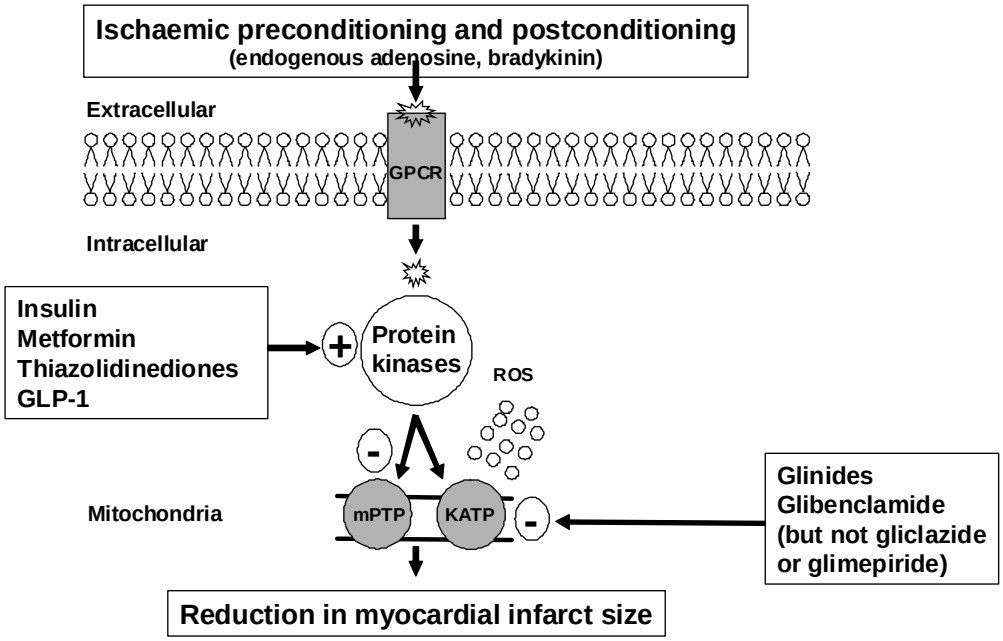

Figure 2. A simplified figure depicting the major components implicated as potential mediators of protection in the settings of ischaemic preconditioning and postconditioning. These include the G-protein coupled receptor (GPCR) activated by endogenous ligands (such as adenosine and bradykinin which are generated during the short bouts of preconditioning myocardial ischaemia), protein kinases (such as Akt, Erk1/2 and PKC), the ATP-dependent potassium channel (K_{ATP}) in the mitochondria, the generation of reactive oxygen species (which themselves activate protein kinases), and the mitochondrial permeability transition pore (mPTP). In addition, the possible sites of action (either activating or inhibiting various components) of various antidiabetic drugs are depicted to portray their potential cardioprotective effects.

to eating, whose synthetic analogues (eg exenatide, pramlintide and lirgalutide) are emerging as potential novel antidiabetic agents capable of stimulating insulin secretion, inhibiting gastrointestinal secretions and motility, and increasing satiety (31).

We and others have recently reported that either recombinant GLP-1 (rGLP-1) (32,33) or its analogue, liraglutide (unpublished data from our laboratory), reduce myocardial infarct size through the activation of protein kinases such as Akt, Erk1/2 or protein kinase A, using a rat heart model of ischaemia-reperfusion injury. Studies suggest that the mechanism of protection of GLP-1 may through its inhibitory effect on the mPTP (34). Importantly, the cardioprotective benefits of GLP-1 have also been examined in the clinical arena of cardiac disease. A small initial study failed to demonstrate improved LV systolic function in patients receiving a 72 hours infusion of rGLP-1 (35). However, a subsequent clinical study in patients undergoing primary PCI (36) found that a 72 hour infusion of rGLP-1, administered at time of PCI, improved LV systolic function in patients presenting with an AMI and impaired LV systolic function (36).

However, one barrier to the therapeutic potential of GLP-1 is that it is rapidly broken down in vivo by dipeptidyl peptidase-IV (DPP-IV) producing an inactive metabolite (31). Further preclinical and clinical studies are therefore required to investigate the cardioprotective potential of DPP-IV inhibitors and other analogues of GLP-1 such as exenatide and pramlintide.

Adipocytokines

White adipose tissue, formerly regarded as purely an energy storage site, is now recognised as an important endocrine organ, producing a variety of peptide hormones, including the "adipocytokines"(37).

Probably the best known of these substances are leptin and adiponectin (38). Other recently discovered adipocytokines, however, include apelin, visfatin and resistin (38,39,40). These substances are involved in the regulation of appetite and energy balance, and abnormalities relating to adipocytokine synthesis may lead to serious metabolic consequences (37,38). Indeed, the adipocytokines have been implicated in various clinical conditions including obesity, diabetes, hyperlipidaemia, hypertension and cardiovascular disease (37,38). More recently it has become evident that the adipocytokines play important roles in the regulation of cardiovascular function (38,39,41).

The 30kDa protein, adiponectin, represents one of the key adipocytokines with respect to metabolism and has been proposed as an anti-atherogenic, anti-diabetic and anti-inflammatory agent (38). Epidemiological studies have revealed that adiponectin correlates negatively with coronary risk (38). Adiponectin produces its physiological actions via the activation of two types of cellular receptors designated AdipoR1 and AdipoR2. Their stimulation in various tissues, including the heart, has been shown to be associated with the activation of AMPK and p38 MAP kinase, cell signalling pathways that have been implicated in cardioprotection (38,42). Adiponectin has also been reported to be mitogenic (42), a feature of cardioprotective agents which activate the Reperfusion Injury Salvage Kinase (RISK) components PI3K-Akt and p44/42, and eNOS (43). AdipoR1 and AdipoR2 are expressed in cardiac tissue and whilst adiponectin has been shown to be produced predominantly by adipose tissue, intriguingly, it has also been found to be synthesised by cardiomyocytes, raising the possibility that adiponectin released by the heart performs an autocrine/paracrine function (44). It has been reported that heart failure is exacerbated in adiponectin-deficient animals and that this is coupled with impaired regulation of AMPK signalling (38). Additionally, it has been demonstrated that adiponectin replacement attenuates myocardial damage (38). Reviewing the data obtained from animal and patient studies led to the proposal that adiponectin may function as an intrinsic cardioprotective agent. It fell, however, to Shibata et al (45) using an in vivo mouse model of ischaemia-reperfusion (I/R) injury to show that adiponectin is, indeed, cardioprotective and that this protection is mediated by AMPK and COX-2-dependent mechanisms. Thus, myocardial infarct size was shown to be increased in adiponectin-deficient (knockout) mice, whilst the administration of

Cardioprotective antidiabetic agents

Antidiabetic agent	Pre-clinical studies	Clinical studies
Insulin	Yes	?
Sulphonylureas (insulin secretagogues)	Block IPC	?harmful
Nonsulphonylurea insulin secretagogues (repaglinide, nateglinide)	?Block IPC	?
Biguanide (metformin)	Yes	Yes
α-glucosidase inhibitors (acarbose)	?	?
Thiazolidinediones (pioglitazone, rosiglitazone)	Yes	Yes
Glucagon-like peptide-1 (GLP-1) analogues (exenatide, pramlintide, liraglutide)	Yes	Yes
Dipeptidyl peptidase-IV inhibitors	?	?

Figure 3. A table highlighting the potential cardioprotective benefits of different classes of antidiabetic drugs as supported by either pre-clinical or clinical studies.

adiponectin reduced infarct size in both knockout and wild-type animals (45). We have also shown that adiponectin delays the opening of the mitochondrial permeability transition pore, which is another property commonly exhibited by cardioprotective agents (unpublished findings).

Leptin, a 16kDa peptide, is a product of the so-called obese (ob) gene (37,38,46). Its receptor (Ob-R) exists as six isoforms, the long, Ob-Rb, isoform appearing to be particularly important physiologically (37,38). With respect to I/R injury leptin has been shown to protect against gastric lesion formation and to reduce I/R-induced injury in the kidney (47,48) An independent association between plasma leptin concentration and heart rate was reported in heart transplant patients and it was suggested that this effect may be mediated through cardiac leptin receptors (49). Subsequently, it was established that the heart does, indeed, express leptin receptors, particularly Ob-Rb (50). The heart was also found to synthesise leptin itself, releasing it into the coronary effluent, raising the possibility that, similar to adiponectin, leptin of cardiac origin may feed back onto the cardiomyocyte to exert a physiological action (51). Leptin has been shown to induce mitogenesis in cardiomyocytes, this action involving the activation of PI3K-Akt and p44/42 (52). As outlined earlier these properties have been proposed as being prerequisites for cardioprotection and, therefore, this prompted us to investigate the putative protective actions of leptin in a Langendorff perfused mouse heart model of I/R injury. Thus, we demonstrated that leptin reduced infarct size via activation of the PI3K-Akt and p44/42 pathways (52). We also showed that leptin delayed the opening of the MPTP. More recently we obtained evidence that the cardioprotective actions of leptin are mediated via the Ob-Rb receptor in the rat heart (unpublished findings).

In addition to leptin and adiponectin we have also investigated the actions of another adipocytokine that is rapidly gaining in prominence, namely apelin (53). Apelin has various isoforms, the most widely studied being apelin-13 and apelin-36, the former invariably being the more biologically active. Apelin and its receptor, APJ, have been detected in various tissues, including the heart (39), and apelin has been reported to activate p44/42, PI3K and p70S6K and act as a mitogen (39). The apelin/APJ system has been implicated in cardiovascular function, acting as a vasodilator and positive inotrope, and has been proposed as a treatment in heart failure (39). We have shown that apelin-13 and, to a lesser extent, apelin-36 reduced infarct size in both in vitro and in vivo mouse models of I/R injury (53). As with leptin, apelin's cardioprotective effects were associated with PI3K-Akt and p44/42 activation, and with inhibition of the MPTP. Therefore our studies (52,53) and those of Shibata et al (45) indicate that the adipocytokines may represent another important group of endogenous cardioprotective substances. Further studies are, however, required to establish if these substances (or appropriate analogues) will prove valuable therapeutically in the context of I/R injury.

Conclusion

Ischaemic preconditioning and the more recently described ischaemic postconditioning represent powerful cardioprotective interventions for reducing cardiovascular morbidity and mortality. Interestingly, the cardioprotective benefits of ischaemic preconditioning and postconditioning, may be harnessed by administering pharmacological agents which activate various components of the pathway implicated in mediating the protection in these setting, such as the protein kinases Akt and Erk1/2. In this regard, certain oral antidiabetic agents such as metformin, the thiazolidinediones, and the adipocytokines, may offer further non-hypoglycaemic benefits to the diabetic patient.

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Submission Deadlines for *The* Bulletin:

Volume	*Date*	*Deadline*
21 (2)	***April 2008***	*1st March*
21 (3)	***July 2008***	*1st June*
21 (4)	***October 2008***	*1st September*
22 (1)	***January 2009***	*1st December*

Secretary's Column

This is my first column as BSCR Secretary, following on from Professor Barbara McDermott who was Secretary of the Society for 6 years. Barbara is a very tough act to follow: my hand-over meeting with her in Manchester left me with 5 pages of closely-written notes on what to do and how to do it! I am sure the whole membership will join with me in thanking her for her huge contribution to the Society's current health and vigour.

Barbara is still very much involved with the nitty-gritty as she is co-organising (with our Chairman, Professor David Eisner) our next meeting, which will be held jointly with the British Cardiovascular Society in Manchester next June. Such joint meetings are particularly tricky to sort out, as evidenced by the 45 minutes the Committee recently spent trying to work out how to incorporate into the meeting Young Investigator awards by both the BCS and the BSCR. Such an apparently small issue turns out to have important consequences for the design and timing of the rest of the meeting, so it is a good job that we have the Secretary Emeritus* and the Chairman involved.

David Eisner's term as Chairman finishes at the end of 2008 (he'll become Chairman Emeritus* at that point), so already we have had to consider who his successor might be. It is the tradition and the rule of the Society that the chairmanship alternates between clinical and non-clinical scientists. The Committee have therefore selected Dr Chris Newman to take over as Chairman from David at the beginning of 2009. This will be put to the membership at the Society's AGM at the Autumn 2008 Meeting. If ratified this means that both Secretary and Chairman will be called Chris. My proposal that the other officer of the Society, our Treasurer Dr Mike Curtis, should also change his name to Chris was regrettably–though narrowly–rejected by the rest of the Committee.

I hope all members enjoyed a peaceful holiday break, and I would like to wish everyone a happy and successful 2008.

*Made-up titles, not formalised within the BSCR Constitution (sorry Barbara and David).

Chris Jackson

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Restitution curves, alternans and ventricular arrhythmogenesis in murine hearts

Ian N. Sabir[1*], Victoria J. Jones[3], Andrew A. Grace[2,3] & Christopher L.H. Huang[1]

Department of Physiology[1] and Biochemistry[2], University of Cambridge, UK; Papworth Hospital[3], Cambridge, UK *correspondence address: ins20@cam.ac.uk

Ian Sabir was awarded the *BSCR Prize* at the Autumn 2007 BSCR Meeting held at St. Thomas' Hospital, London

Beat-to-beat alternation in cardiac action potential duration (APD), termed *alternans*, has been associated with ventricular arrhythmia for over a century (Traube, 1872). To this day the presence of alternans on the electrocardiogram remains, in some situations, the strongest predictor of arrhythmic risk available without the employment of invasive electrocardiological techniques (Gold *et al.*, 2000). The possible intervening mechanisms linking alternans to arrhythmia are covered in detail elsewhere (Weiss *et al.*, 2006). In a recent publication we demonstrated such alternans occurring in association with ventricular arrhythmia in murine hearts for the first time (Sabir *et al.*, 2007a). Thus while hearts mounted on Langendorff apparatus and perfused with normokalaemic Krebs-Henseleit solution demonstrated stable APDs and stable rhythms, hypokalaemic hearts developed arrhythmia (Figure 1) following periods of alternans (Figure 2).

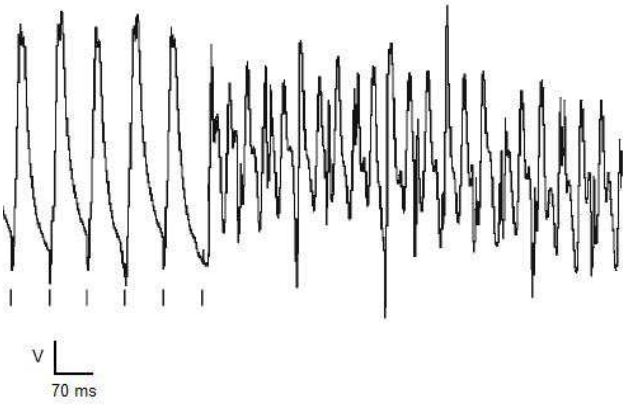

Figure 1: Epicardial monophasic action potential recordings obtained from a murine heart perfused with hypokalaemic (3.0 mM K^+) solution. Vertical lines denote stimuli.

Various mechanisms have been proposed to underlie alternans in such situations. Recent attention has focused on altered Ca^{2+} handling by the sarcoplasmic recticulum (Walker *et al.*, 2003). However, alternans has most often been described using the elegant analysis first proposed by Nolasco & Dahlen (1968). This considers relationships between APD and diastolic interval (DI, see Figure 3, inset). It is well established that APD is strongly influenced by the preceding DI, $APD_n = f(DI_{n-1})$ as illustrated by the solid, *restitution curves* in Figure 3. However, at any given heart rate, the resulting baseline cycle length (BCL) is necessarily the sum of the APD and DI. DI is then directly determined by the preceding APD through relationships of the form $DI_{n-1} = f(APD_{n-1}) = BCL - APD_{n-1}$. These relationships are illustrated by the broken lines in Figure 3 which each represent a different BCL.

At any stable, steady-state BCL, APD will be given by the point of intersection between the restitution curve and the appropriate broken line. This analysis then provides a potential basis for alternans to arise as a result of an alteration in BCL, such as stepping from the long BCL represented by broken line *i* to the shorter BCL represented by broken line *ii* (Figure 3a). As always, the duration of the subsequent action potential will be determined by the preceding DI. This preceding DI will be determined both by the new BCL and by the preceding APD, which will have been determined by the previous, longer, DI resulting from the previous, longer, BCL. This will ultimately result in a shorter-than-expected DI and thus a shorter-than-expected subsequent APD. Considering the next beat, APD will of course be determined by the preceding

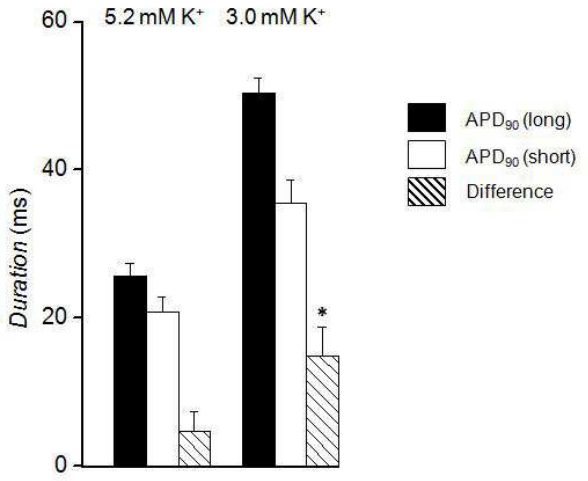

Figure 2: Successive long (filled bars) and short (open bars) epicardial monophasic action potential durations and the difference between these values (hashed bars) obtained from murine hearts perfused with normokalemic (5.2 mM K^+) and hypokalaemic (3.0 mM K^+) solutions.

DI. This will, in turn, depend on the new BCL and on the previous APD, which was shorter-than-expected. Thus the new DI will be longer-than-expected, resulting this time in a longer-than-expected subsequent APD. The result is an alternans that could lead to one of two possible outcomes dependent upon the slope of the restitution curve. In the event that the gradient of the restitution curve in the region over which the alternans occurs is < 1 (a > b, left-hand panel in Figure 3), successive iterations result in a *convergence* of the APD to a new equilibrium point given by the point of intersection of the restitution curve and broken line *ii*. In contrast, if the gradient over this range is > 1 (a < b, right-hand panel in Figure 3), successive iterations lead to a progressive *divergence* of APD and alternans of a progressively greater and greater magnitude. Our recent experiments vindicate this analysis, associating increased slopes of restitution curves with alternans and arrhythmia in hypokalaemic murine hearts (Sabir *et al.*, 2007a) (Figure 4).

Recent studies have associated such steeply sloping restitution curves with ventricular arrhythmia in human sufferers of the Brugada syndrome (Narayan *et al.*, 2007; Nishi *et al.*, 2007). Since mice offer unique opportunities for the introduction of genetic modifications they are highly amenable to the study of such hereditary arrhythmic disorders. Thus we recently demonstrated that *Scn5a*+/- murine hearts modelling the Brugada syndrome demonstrate similarly steeply sloping restitution curves (Figure 5, left panel) in association with arrhythmogenicity (Sabir *et al.*, 2007b). Given the current controversy surrounding risk-stratification

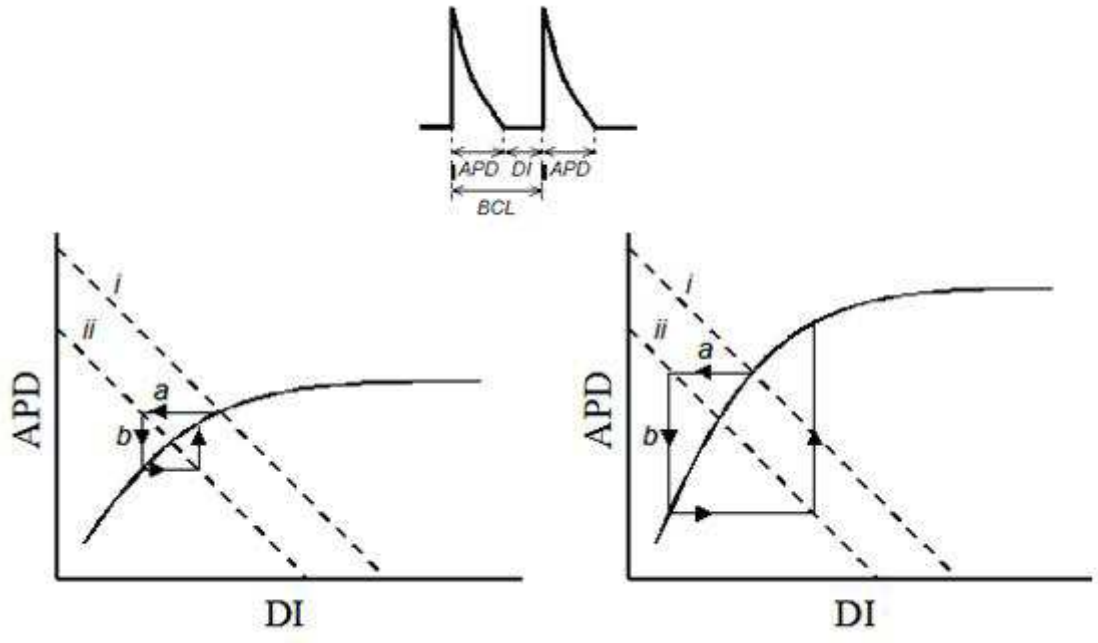

Figure 3: Restitution curves (solid lines) showing experimentally-determined relationships between action potential duration (APD) and preceding diastolic interval (DI). Dashed lines show relationships between diastolic interval and preceding action potential duration. Inset graphically depicts APD, DI and baseline cycle length (BCL).

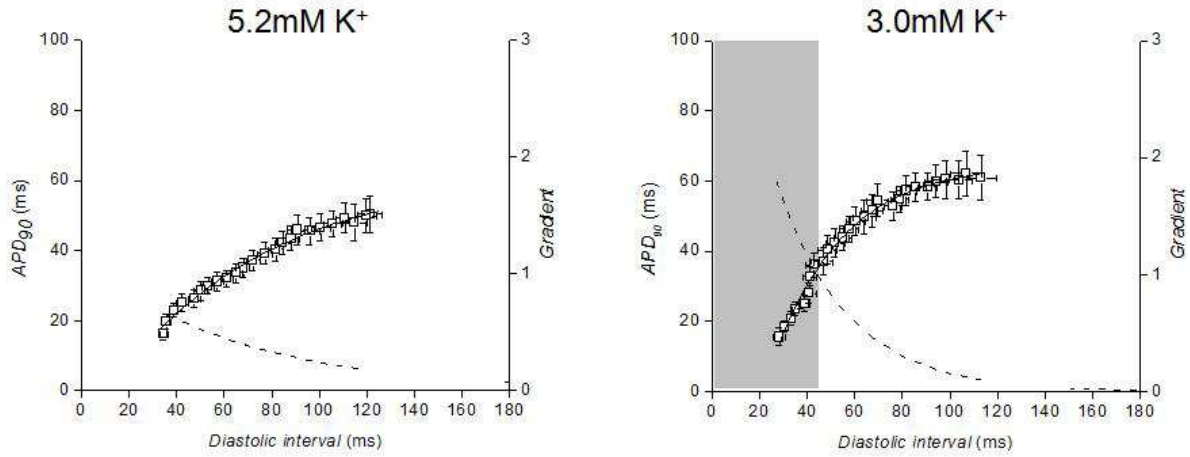

Figure 4. Restitution curves relating action potential duration to diastolic interval (solid lines, left-hand axes) and corresponding gradients (broken lines, right-hand axes) obtained from normokalemic (5.2 mM K+) and hypokalaemic (3.0 mM K+) murine hearts. Grey regions where present indicate the range of diastolic intervals over which the gradient of the restitution curve exceeds unity.

in the Brugada syndrome (Paul *et al.*, 2007), it is possible that restitution curves may in the future have a useful contribution to make. We thus went on to demonstrate not only that flecainide is pro-arrhythmic in *Scn5a*+/- murine hearts, recapitulating human observations (Brugada *et al.*, 2000), but also that this effect is associated with increases in the slopes of restitution curves (Figure 5, centre panel). While the pro-arrhythmic effect of flecainide in the Brugada syndrome is well-established, the potential for quinidine to exert an anti-arrhythmic effect remains controversial (Belhassen *et al.*, 2004). Nevertheless, in our study, not only was quinidine anti-arrhythmic but this effect was associated with decreases in the slopes of restitution curves (Figure 5, right panel). These experiments may thus shed light on the means by which flecainide and quinidine exert their effects in sufferers of the Brugada syndrome. It is thus possible that restitution curves may in the future prove useful in assessing the potential utility of novel anti-arrhythmic agents in such settings.

Although alternans and restitution curves are well-worn concepts in cardiac electrophysiology, these ideas remain highly relevant in addressing emerging translational issues in both basic science and clinical practice.

We thank the James Baird Fund, the Frank Elmore Fund, the Medical Research Council, the Wellcome Trust, the British Heart Foundation and Downing

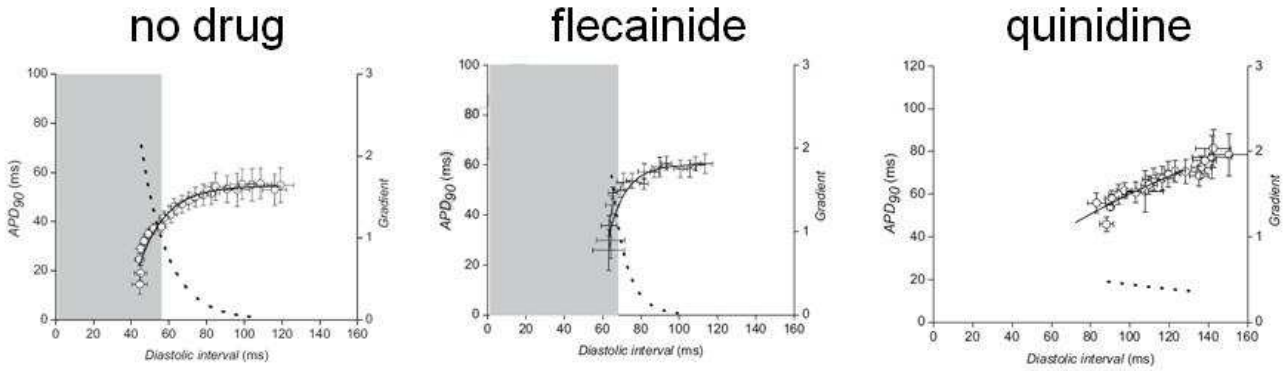

Figure 5: Restitution curves relating action potential duration to diastolic interval (solid lines, left-hand axes) and corresponding gradients (broken lines, right-hand axes) obtained from Scn5a+/- murine hearts treated with control solution (left) and solutions containing 1 ì M flecainide (centre) and 10 ì M quinidine (right). Grey regions where present indicate the range of diastolic intervals over which the gradient of the restitution curve exceeds unity.

College, Cambridge for their generous support. Figures 1, 2, 4 and 5 are reprinted from Sabir et al. (2007a) and Sabir et al. (2007b) with the kind permission of Springer Science and Business Media.

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Articles for *The* Bulletin

Would you like to write a Review or Laboratory Profile for the BSCR Bulletin? These articles provide an excellent opportunity to let BSCR members know about your research activities and also provide an insight into your research field.

We are keen to hear from anyone in cardiovascular research who would be willing to write for *The* Bulletin.

If you are interested, please contact the Bulletin editors with your ideas: Helen (h.maddock@coventry.ac.uk) or Nicola (N.Smart@ich.ucl.ac.uk)

Vascular Calcification:

A BSCR Symposium Report and viewpoint

by Dr M. Yvonne Alexander, University of Manchester

The annual conference of the British Cardiovascular Society 2007 was held at the SECC Glasgow on June 5th – June 7th. The BSCR, being an affiliate group of the BCS, are invited each year to present a short symposium at the BCS annual conference. This year the topic chosen for presentation was "Molecular and clinical aspects of vascular calcification: - prognostic and therapeutic implications", and was organised by Yvonne Alexander (Cardiovascular Research Group, University of Manchester).

The BCS has traditionally been a clinically orientated and drug-sponsored group, but with the recent drive for translational medicine, the continuing contribution of BSCR is recognised as being an excellent resource for the scientific content of the conference. Sponsorship for the meeting was received from Astra Zeneca, Zeiss, Wolf, PAA Laboratories, Promocell and Anachem enabling the provision of some warm hospitality to the speakers by way of an enjoyable and friendly "Welcome to Glasgow" dinner in the renowned Ubiquitous Chip.

Yvonne co-chaired the session with Professor Peter Weissberg, Medical Director of the British Heart Foundation, who introduced the first speaker Professor Paolo Raggi MD, FACP, FACC, from Emory University, who, in his role as Professor of Medicine-Cardiology and Professor of Radiology, provided an excellent overview of the recent advances in our understanding of vascular calcification. Paolo described the recent developments in imaging technology such as multi-row detector computed tomography (MDCT) as a precise non-invasive imaging modality for quantifying calcification. These developments have made it possible to conduct population-based investigations into its use as a prognostic tool for an unfavourable cardiovascular outcome. The studies have demonstrated a definitive link between calcium burden and the future occurrence of cardiovascular events.

Paolo discussed the recent data from trials investigating the risk of death in hemodialysis patients who were being treated with phosphate control interventions. Patients on haemodialysis experience a much greater mortality rate than in the general population and dialysis patients commonly exhibit more vascular calcification (VC) than age- and gender-matched controls without kidney disease. Phosphate plays a causative role in the development of vascular calcification in renal failure, and these studies have shown that treatment with calcium-based phosphate binders can further increase the Ca x PO_4 product, adding to the risk of ectopic mineralization. However, the new calcium-free phosphate binders, sevelamer and lanthanum, appear to control hyperphosphatemia without adding to the patients' calcium load. Given the clinical coincidence of vascular calcification in patients with osteoporosis, it has been suggested that common regulatory molecules can adversely affect both bone metabolism and vascular integrity. The bisphosphonates are inhibitors of bone resorption that are widely used to treat osteoporosis and are considered protective against vascular calcification through their effects on the inhibition of osteoclastogenesis (Figure 1A). A cytokine that plays a key role in bone resorption is the receptor activator of nuclear factor-kappa B ligand (RANK-L). It acts through the receptor activator of NF-kappaB (RANK), (Figure 1A) while osteoprotegerin (OPG) acts as a decoy receptor that binds RANK-L, preventing activation of RANK, (Figure 1B). In the case of bone deposition in the vessel wall, with the excess calcium and mineral being released from bone, it is thought that signalling events trigger an osteogenic differentiation programme whereby progenitor-like cells residing in the vessel wall differentiate into osteoblast-like cells and deposit a mineralised matrix (Figure 1C). Protection against mineralisation in the vessel wall is achieved by cells increasing their expression of OPG and RANKL, which inhibits osteoclast maturation and prevents the subsequent release of calcium and mineral from bone (Figure 1C). Trial evidence indicates that the RANK-L blocking monoclonal antibody denosumab increases bone mineral density in osteopenic postmenopausal women. Therefore the RANKl/OPG signalling system could be a common link in physiological and pathological processes that affect both vascular and skeletal systems.

The next talk by Dr Veerle Persy (University of Antwerp, Belgium) entitled 'Boning up on rat arteries: detection, quantification and intervention in experimental vascular calcification.'highlighted the parallels of vascular calcification to bone formation and a

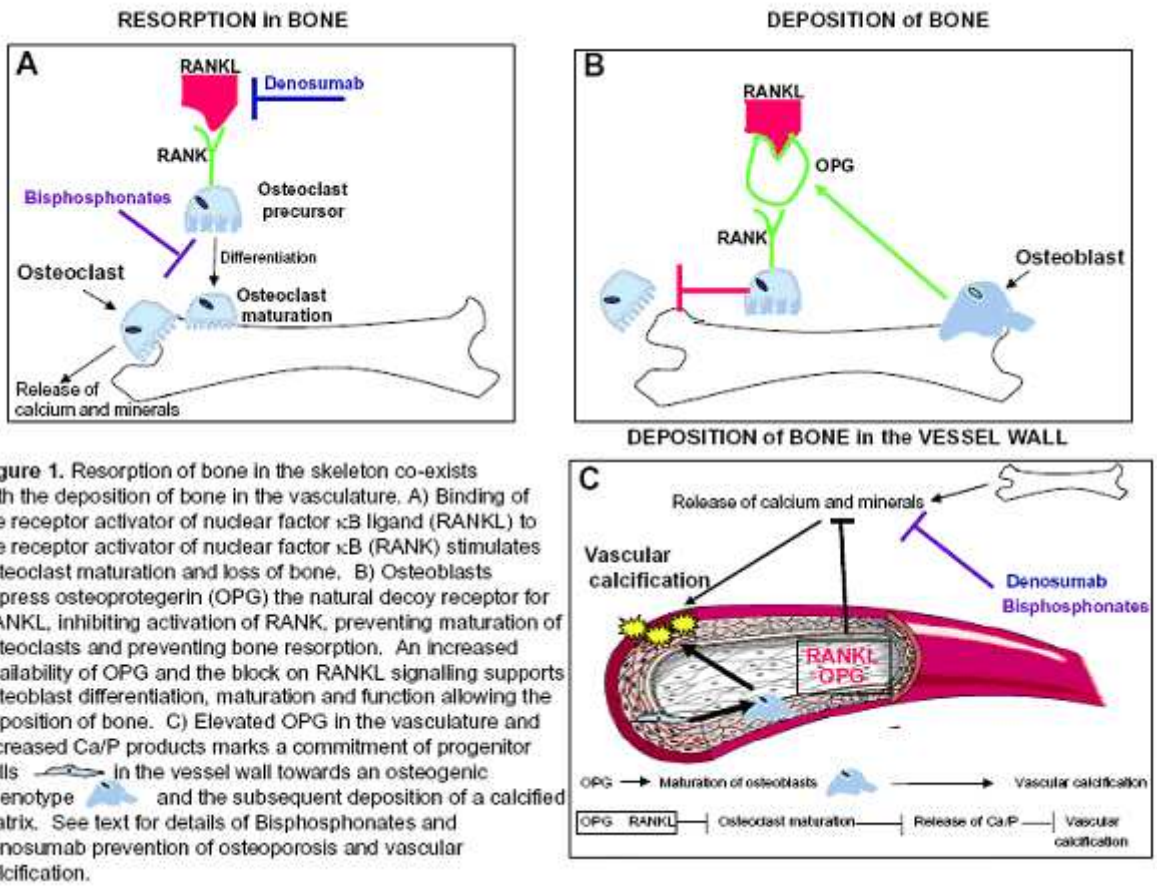

Figure 1. Resorption of bone in the skeleton co-exists with the deposition of bone in the vasculature. A) Binding of the receptor activator of nuclear factor κB ligand (RANKL) to the receptor activator of nuclear factor κB (RANK) stimulates osteoclast maturation and loss of bone. B) Osteoblasts express osteoprotegerin (OPG) the natural decoy receptor for RANKL, inhibiting activation of RANK, preventing maturation of osteoclasts and preventing bone resorption. An increased availability of OPG and the block on RANKL signalling supports osteoblast differentiation, maturation and function allowing the deposition of bone. C) Elevated OPG in the vasculature and increased Ca/P products marks a commitment of progenitor cells in the vessel wall towards an osteogenic phenotype and the subsequent deposition of a calcified matrix. See text for details of Bisphosphonates and denosumab prevention of osteoporosis and vascular calcification.

remodelling process. Her data suggested a cell-regulated process resembling endochondral ossification (via a cartilage template). She demonstrated the presence of cells expressing chondrocyte-specific markers sox9, collagen II, in rat arteries with severe media calcification, indicating the presence of cartilaginous metaplasia. She also showed the de novo expression of a key osteogenic marker, core-binding factor alpha1 (cbfa1). Her studies involved the use of a rat model of chronic renal failure (CRF), induced with a diet supplemented with adenine and then she confirmed her findings in tissue from human transplant donors. Clearly, the findings of osteoblast-like, chondrocyte-like and osteoclast-like cells in the calcified aortic tunica media of uremic rats, fuels the debate on the mechanisms behind the "calcification paradox" - disturbed bone turnover in association with ectopic mineralisation.

Dr Adrian Chester (University London Imperial College) followed on, with his presentation on the "Molecular and cellular studies of cardiac valve calcification", highlighting the problems of calcification in the context of aortic valve disease, which for many years was thought to be due to calcium deposition on the surface of the aortic valve leaflet. However, the etiology of this disease is now recognised to be similar to vascular calcification and is associated with inflammatory changes and expression of osteoblast-related genes. Adrian demonstrated the involvement of extracellular nucleotides, in particular ATP, in inducing osteoblast differentiation using human valve interstitial cells as an *in vitro* calcification model. He then went on to suggest a potential mechanism by which statins may exert anti-calcifying properties by showing that atorvastatin degraded extracellular ATP into adenosine which inhibited the ATP- induced activity of an osteoblast marker, alkaline phosphatise (ALP).

Finally there was a presentation from Dr. William Jeffcoate (City Hospital, Nottingham) who talked about "Factors involved in the pathogenesis of arterial calcification in diabetes". His life's work in the diabetes clinic enabled him to provide some insights into the paradoxical occurrence of vascular calcification and bone loss in patients with diabetes and peripheral neuropathy, and especially in those with Charcot neuroarthropathy (CNA) - a serious complication, associated with increased bone resorption and destruction of foot architecture. In patients with diabetes, there are data linking vascular calcification with increased mortality and we heard, this time in the

context of diabetes, of an accentuation of the Receptor Activator of Nuclear factor Kappa-B-Ligand/ osteoprotegerin (RANK-L/OPG) signalling pathway.

The take-home message from the symposium was the fact that there is no single theory to describe the aetiology and pathogenesis of vascular calcification. Many factors have been implicated in the deposition of a mineralised matrix in the vessel wall including i) a change in gene expression in smooth muscle cells driving them towards an osteogenic phenotype, ii) a release of cytokines and growth factors that influence vascular cell dynamics, iii) smooth muscle cell apoptosis, iv) an increased deposition of extracellular matrix, as well as v) alterations in mineral metabolism. Although there is limited clinical management of vascular calcification; we are beginning to unravel some of the molecular and cellular mechanisms underpinning this process, allowing us to get a little closer to understanding the nature of this devastating pathology, opening the potential for the development of future pharmacological interventions.

We would like to thank the speakers and chairs and particularly the event organisers, Mary-Lou Pitts and Tony Cavalheiro and we also gratefully acknowledge our sponsors. Such is the success of these small BSCR symposia within the larger BCS annual conferences, that next year it has been decided that the BSCR Spring meeting will be postponed to the Summer and will be run jointly with the BCS Annual Scientific Conference in Manchester on June 2nd – 3rd 2008.

Autumn 2007 BSCR meeting : The QT interval and drug-induced torsades de pointes

St Thomas Hospital, London

24th-25th September 2007

A report by Dr Mike Curtis, Meeting Organiser

It was pleasing for me, a pharmacologist, to offer the BSCR a meeting this year that was concerned with the actions of drugs. More than 90 delegates plus speakers attended this highly focused meeting, which was divided into three sessions over two days. The topic was validation of biomarkers, risk factors and preclinical investigational methods for the detection of drug-induced torsades de pointes (TDP) liability.

The first of the three symposia offered a unique forum to address an issue of controversy - whether QT prolongation is a sufficient and necessary biomarker for attributing a TDP liability to a drug. The plan was to engage two internationally recognised proponents of differing viewpoint (Luc Hondeghem and Dan Roden) with each of them presenting their case in a talk (30 min). The speakers were then to submitted themselves to a panel of six experts (Gary Gintant, Marc Vos, Jules Hancox, Russ Bialecki, Leif Carlsson, and Rashmi Shah) who, under my chairmanship, would lead an audience participation debate. This plan worked in as much as the talks were given and issues were discussed. However it transpired that the second speaker agreed "98%" with the perspective of the first speaker. This meant that rather than the hoped-for 'heated debate', the relative harmony allowed wider issues to be elaborated. The whole event was audiotaped with a view to transcribing and publishing the essence of the debate at a later date. Presently, the expert panel members, together with the chairman moderator are preparing a manuscript. Neither speaker 1 nor speaker 2 will participate in this or be part of the authorship. The article was initially intended to effectively make a judgement on the arguments presented by the speakers but, since the arguments did not differ, this is now precluded.

The two other symposia took a more conventional line, allowing opportunity for speakers to exercise their own agenda. The second symposium was entitled "How validated are current models and biomarkers for testing drug-induced torsades de pointes liability?" Speakers were asked to examine the validation of their chosen biomarkers for TDP liability. Validation, as far as this symposium was concerned, meant that the endpoint measured in the method predicts

TDP liability specifically, selectively and quantitatively. Few, if any, method is truly validated so the speakers were instructed to explore the limits of the validation of their chosen method. Topics (and speakers) included: human volunteer phase 1 studies (Torbjörn Vik); the anaesthetized rabbit TDP model (Leif Carlsson); the AV blocked canine preparation (Marc Vos); QT interval and its corrections in the in vivo conscious canine (Anthony Fossa); the rabbit heart failure model (Bob Hamlin); the rabbit Langendorff preparation and the Screenit approach (Berengere Dumotier); the wedge preparation (Gan-Xin Yan) and HERG screens (Jules Hancox). Unbeknownst to the speakers before the start of the sessions, the audience were invited, during the session introduction, to rate each approach on a 0 to 10 scale in terms of the extent to which each approach appeared to be validated. The outcome of this exercise will be published in due course.

The final session was entitled: "Drug-induced torsades de pointes - now what?" This symposium focused on individual separate cutting-edge issues. Topics included: Should preclinical TDP liability assessment take into account the influence of channelopathies? (Craig January); a drug for men and women - how important is gender as a TDP disposition risk factor? (Susan Coker); inter-model comparisons - the experience of the QT Prodact initiative (Keitaro Hashimoto); are any of the preclinical TDP screens good for quantitative (dose-response) TDP liability assessment? (Gary Gintant); if a drug deemed 'safe' in preclinical tests subsequently prolongs QT in phase 1 studies how can its developer convince regulators to allow development to proceed? (Rashmi Shah) and preclinical cardiovascular safety assessment - is this a career for new cardiovascular PhD graduate? (Michael Pugsley).

The second and third symposia will be published in 2008 in a focused issue of the review journal Pharmacology and Therapeutics, with the results of the audience survey included in an editorial.

The conference dinner was held in a hotel adjacent to the meeting venue. It was well attended, and offered a good opportunity for conversation.

The meeting was sponsored by generous educational grants from the British Heart Foundation, Abbott USA, Astrazeneca USA, Janssen Pharmaceuticals Belgium, QTest Labs USA and Servier France.

I am indebted to Tony Cavalheiro who managed the pre-meeting logistics, and to my research group (Catherine Stables, Ellen Andrag and Abi Rickard) who worked tirelessly to ensure the meeting ran smoothly.

Michael Davies Early Career Award for contribution to Cardiovascular Science

This award from the British Cardiovascular Society is to honour researchers who have recently established themselves as independent investigators and who have made an outstanding contribution to cardiovascular science.

The scheme is open to clinicians and non-clinicians who have an affiliation with a UK institution. The award of £1500 and a certificate, will be made at the Annual Scientific Conference of the BCS and the successful candidate will be expected to give a 20-min oral presentation of their work at that meeting.

A single award will be made each year.

Eligible are researchers who have shown sustained outstanding productivity over several years, resulting in a significant contribution to cardiovascular science. They are expected to be typically within 5-10 years of achieving their higher degree and to be on track to continue a successful academic career.

Deadline for applications is the 31st of January 2008.
Full application details can be found on the BCS website: http://www.bcs.com

Travel Report: American Heart Association Scientific Sessions 2007

Orlando, Florida, USA

Pre-Session Symposia: 3rd November; Scientific Sessions: 4th - 7th November

by Dr Fleur Moseley, School of Pharmacy, University of Reading

The American Heart Association's (AHA) Scientific Sessions is the world's largest annual convention targeting both scientists and healthcare professionals with an interest in cardiovascular disease and stroke. This year, the convention was hosted in the palatial and impressive Orange County Convention Centre in Orlando, Florida. The organisers expected to host approximately 26,000 attendees over the four

AHA Scientific Sessions 2007 welcomed over 26,000 delegates for the 4 day convention

day conference. The event included nearly 3,800 abstracts of original research and around 1,300 invited presentations covering a huge range of topics, broadly divided into the areas of clinical, basic and population science, as well as, some highlighted plenary and special sessions providing an opportunity to learn about state of the art cardiovascular research and how it applies to clinical practise. This year also hosted the AHA's first International Congress on stem cells and myocardial regeneration, which brought together leading experts in the field and provided a platform to share new technologies and data, and to discuss the complexities of this field of research.

The Pre-Session Symposia was held on 3rd November as an introduction to the International Congress, and itself was divided into two sessions: entitled - "Stem cells and prevention of cardiovascular diseases: If I can stop one heart from breaking" and "Debate: Cell therapy for the failing heart". The first half of the symposia provided a good overview of the current position of stem cell research and included presentations on myocyte survival (Mark Sussman, San Diego, US); mechanisms of cell death and survival (Junichi Sadoshima, Newark, US); cardiac stem cells (Piero Anversa, Valhalla, US); amplification of cardiac myocytes (Steven Houser, Philadelphia, US); electrophysiological regeneration of the conduction system of the heart (Lori Gepstein, Haifa, Israel); and, the plasticity of epithelial progenitor cells (Stephanie Dimmler, Frankfurt, Germany).

Dr Sussman gave an interesting presentation discussing approaches to promote cardiac myocyte cell survival by manipulating the signalling pathways involved

The Exhibit Hall showcased a vast range of emerging technologies, healthy lifestyle programs, hands-on learning and publishers

Some of the thousands of posters presented over the 4 days

in apoptotic cell death. He highlighted the importance of Pim 1, a signalling molecule downstream of Akt signalling with anti-apoptotic effects and showed data suggesting that Pim 1 was involved in cell survival, maintaining mitochondrial integrity, physiological calcium handling, prevention of maladaptive hypertrophy, stem cell proliferation as well as the secretion of beneficial cytokines, mediating trafficking, survival and differentiation of stem cells to the damaged heart.

Dr Anversa talked about their recent work addressing the criticisms of their initial reports that documented the presence of new cardiac myocytes in the infarcted heart following the injection of bone marrow-derived stem cells (BMSCs). Concerns about autofluorescent artefacts, donor-recipient cell fusion and the lack of adequate genetic markers to determine host origin had been addressed in their recent work and data from a series of experiments was presented. The study used several approaches including gene reporter assays, genetic tagging and direct immunofluorescence with quantum dots and demonstrated the engraftment of BMSCs into the damaged heart and transdifferentiation of these cells into cardiac myoycytes. The study concluded that injection of BMSC was able to generate de novo myocardium and that this was independent of cell fusion.

The next session summarised results from several phase I and phase II clinical trials investigating the therapeutic potential of various stem cell populations such as BMSCs, allogenic mesenchymal stem cells and skeletal myoblasts. This included the phase II trials; REPAIR-AMI (BMSC) presented by Andreas Zeiher (Frankfurt, Germany); AST-AMI trial (BMSC) described by Ketil Lunde (Oslo, Norway); BOOST 1 and 2 trials (BMSC) detailed by Helmut Drexler (Hannover, Germany); and, the MAGIC trial (skeletal myoblasts) described by Robert Michler (New York, US). The clinical relevance of stem cell mobilisation was also examined by the REVIVAL 2 trial which investigated G-CSF therapy and was presented by Dretlind Zohlnhoeter (München, Germany). All of the trials found that the treatments were safe and the majority demonstrated that cell therapy did confer some beneficial effects on heart function following treatment; however, these differences had not been as pronounced as initially had been hoped. On average, BMSC therapy is associated with an improvement in ejection fraction in the region of 2.5- 2.8 % (Helmut Drexler, Hannover, Germany) but this was not associated with improvements in left ventricular end diastolic or systolic volumes. They also highlighted the presence of conflicting findings with some trials (AST-AMI) reporting a lack of clinical benefit with cell therapy. Additionally, a lack of basic understanding regarding precise characterisation of stem cell preparations, their transdifferentiation capacity and their long term clinical capabilities also became apparent. Although clinical trials have shown that cell therapy does not have detrimental effects on patient health and survival, questions still remain regarding the "best" cell type to

The impressive interior of the Orange County Convention Centre

use and the mechanism by which these cells exert their effect. The ability of BMSCs to transdifferentiate into cardiac myocytes is still the matter of hot debate and, as such, it remains unclear whether BMSCs are able to directly contribute to myocardial mass or whether beneficial effects are due to revascularisation, cell survival, alterations immune or inflammatory responses or other paracrine factors. It became apparent that more basic research is required rapidly, particularly as cell

therapy has already reached the clinic and debate reigned as to whether new trials should be initiated without prior advances in our understanding of basic stem cell biology.

Stem cell symposia dominated the basic science programme; nonetheless, there were many other interesting presentations that could not be missed. In particular, was a presentation given by Thomas Matthiesen from University of Minnesota, during a session entitled "Cardiac Regeneration/Cell Therapy - Experimental: Tissue engineering and Cardiac repair". The session highlighted scaffolding options for tissue engineering, including both micromoulded patches (W.Bian, Duke University, Durham, US; M. Louis Tisserand, INSERM, France) and self-assembly nanopeptides which polymerise in vivo providing a matrix to deliver a range of factors into the injured heart. Dr Matthiesen discussed a new method for creating biocompatible 3D scaffolds for engineering cardiovascular tissues, including the heart, lung and kidney. He presented data which had utilised cadaver organs as a source of 3D scaffolds providing perfect physiological structure. By perfusing organs with detergents, decellularised tissue, retaining only the native extracellular matrix, was obtained. This decellularized tissue retained the anatomy and ultrastructure of the original organ with less than 2.2 % of cadaveric DNA remaining. Recellularisation of the scaffold had been attempted using the rat as a model and Dr Matthiesen showed an impressive video of a beating heart in vitro that had been generated by perfusing the scaffold with neonatal cardiac myocytes over a 4-day period. The best source of cells for recellularization is yet to be determined but stem cell populations appeared to be at the forefront of their approach. Although this technology is clearly still in its infancy, it did demonstrate that decellularization of cadaveric organs does provide a biocompatible scaffold which is conducive for cell growth and viability and might provide a useful source of whole organs for transplant in the future.

Another highlight of the conference was the session on proteomics, entitled "Bringing Proteomics to the Clinic" which included presentations on new technologies for proteomic analysis (Daniel Knapp, Charleston, US), in combination with a series of seminars presenting data from a number of projects aiming to identify biomarkers of disease or novel therapeutic targets, using proteomic techniques (including, Lorraine Ware, Nashville, US; Frank Accurso, Denver, US; and, Robert Gertszten, Boston,

The magnificent West Chapin Theatre, which was host to the "special sessions" series of presentations during the conference

US). The session emphasised the difficulties of working with blood, in particular for biomarker studies, due to its vast dynamic range in protein abundance, and discussed potential avenues for simplifying the sample by removing the abundant proteins, such as albumin, or by specifically binding proteins of interest. However, it also was stressed that by removing such proteins you are likely to remove proteins that are associated with them, which might be those of interest. The importance and difficulty of target validation was evident and a point that was raised on several occasions, particularly in light of the lack of suitable antibodies, high throughput multiplex ELISA assays and suitable clinical datasets. Several presentations showed data utilising combinations of biomarkers, as opposed to a single marker, to assist clinical diagnosis or prognosis and concluded that this was a more effective approach. The potential of using such markers to identify patients likely to respond to specific treatment regimes was also discussed. The

Dr Katrina Bicknell (left) and Dr Fleur Moseley ride "The Kraken" at SeaWorld. 4177 feet long, 144 foot drop, 7 inversions and speeds of 65 mph!

conclusion of the session was that the present proteomic technologies available for research are far from ideal, each possessing strengths and weaknesses, but current methods are able to identify candidate biomarkers for disease although stringent target verification and validation is required.

On a lighter note, you cannot travel all the way to Orlando without experiencing one of its favourite attractions in the beautiful Florida sunshine. We chose to take a trip to Seaworld, the home of Shamu, the Killer Whale, their prime attraction. It provided the perfect avenue to reflect on the conference and to give the grey matter a well-deserved rest! We experienced some fantastic shows involving a range of sea creatures, including the dramatic Shamu show. We made the mistake of positioning ourselves in the empty seats close to the front in the "wet" zone, which now I suggest should be re-named the "completely soaked to your skin" zone. This was followed by my sensible suggestion to try out the huge rollercoaster, called The Kraken, in an attempt to dry off! Indeed we were dry when we got off the roller coaster, but now suffered from high blood pressure and were a risk of a heart attack ourselves. I have included the photo, which illustrates the effects of the rollercoaster beautifully.

Overall, I found the AHA scientific session an interesting and compelling conference. I was overawed by the scale of the convention and to the extent of cardiovascular research taking place around the world. It provided a great opportunity to get up to date on leading research in my field of interest, as well as, proving a good avenue to become familiar in new scientific areas. Next year's conference is to be held in New Orleans, Louisiana, and I am sure it will be equally successful, enabling scientists to discuss ideas and share their interests and developments in cardiovascular research.

Cardiovascular Meetings

American Heart Association International Stroke Conference 2008 to be held at Ernest N. Morial Convention Center - New Orleans, LA, USA on Feb 20-22, 2008. For further information, please refer to the meeting website: http://strokeconference.americanheart.org/portal/strokeconference/sc/

AHA Arteriosclerosis, Thrombosis and Vascular Biology Annual Conference 2008 will be held at Omni Hotel at CNN Center - Atlanta, GA on Apr 16-18, 2008. Contact: E-mail: scientificconferences@heart.org; Phone: (888) 242-2453 or (214) 570-5935

XXVIII European Section Meeting of the ISHR will be held on 28-31 May 2008, Athens, Greece. Further information can be obtained from www.ishr-greece2008.gr. Panos Travel Ltd - Attn: ISHR 2008 Phone: +30/2109962500; Fax: +30/2109969245 E-mail: ishr2008@panos-travel.gr

Heart Failure 2008 Congress, 14 June 2008 - 17 June 2008 Milano Convention Centre, Milan, Italy Further Information is available from: Heart Failure 2008 Secretariat, ESC - European Heart House, 2035 Route des Colles, Les Templiers - BP 179, 06903 Sophia Antipolis Cedex, France Tel: +33 (0)4 92 94 76 00; Fax: +33 (0)4 92 94 76 01

XXX Annual Meeting of the North American Section of the ISHR. Hilton Cincinnati, Netherlands Plaza, Cincinnati,OH. June 17-20, 2008. Enquiries: Dr Litsa Kranias, litsa.kranias@uc.edu; Dr Jeffrey Robbins, jeff.robbins@cchmc.org

AHA Basic Cardiovascular Sciences Conference 2008 - Heart Failure: Molecular Mechanisms and Therapeutic Targets will be held at Keystone Conference Center - Keystone, CO on 28-31 July, 2008. For further information: E-mail: scientificconferences@heart.org; Phone: (888) 242-2453 or (214) 570-5935

ESC Congress 2008, 30 August 2008 - 03 September 2008 Messe München, Germany. Further information, when available can be found at: http://www.escardio.org/

British Heart Foundation Grants

CHAIRS AND PROGRAMME GRANTS COMMITTEE AUGUST 2007

Programme Grants

Professor K Clarke et al, University of Oxford. "Substrates, transcription and control of cardiac energy metabolism and function" 5 years (renewal; years 11-15) £1,347,387

Professor A F Dominiczak et al, University of Glasgow. "Genomics and proteomics of hypertension and its vascular complications: the pathwayomic strategies" 3 years (renewal; years 11-13) £814,662

Professor JRF Paton et al, University of Bristol. "Vascular-neuronal signalling in the nucleus tractus solitarii: novel implications for blood pressure control" 5 years (renewal; years 6-10) £782,494

Dr D J Henderson et al, University of Newcastle upon Tyne. "Integrating mechanical and physical forces into the regulatory network of heart morphogenesis" 5 years (renewal; years 6-10) £858,173

Professor Sir M G Marmot et al, University College London. "Psycho-social and biological factors in the occurrence of cardiovascular disease: The Whitehall II study" 5 years (renewal; years 6-10) £1,023,519

Special Project Grant

Professor J E Deanfield et al, University College London. "Adolescent type 1 diabetes cardio-renal intervention trial (AdDIT)" 5 years, £998,635

Medical Research Council, London. "Biomarker Awards" (joint funding with Medical Research Council) £1,000,000

Professor A D Struthers et al, University of Dundee. "The potential to improve primary prevention by using BNP as an indicator of silent pancardiac target organ damage: the 5P study" 5 years £323,958

Professor P J Talmud et al, University College London. "The integration of the knowledge of genes involved in heart development and cardiovascular processes from biomedical research, using standardised gene ontology" 5 years £541,785

PROJECT GRANTS COMMITTEE JULY 2007

DEFERRED APPLICATIONS AWARDED

Dr D P Francis et al, Imperial College London. "Developing a new, dynamic, therapeutic pacemaker algorithm for stabilising periodic breathing in chronic heart failure" (3 years) £238,850

Dr D P Francis et al, Imperial College London. "Assessment of right ventricular function during and following cardiac surgery and evaluation of pericardial physiology in preserving RV function" (3 years) £181,450

NEW APPLICATIONS AWARDED

Prof J C Kentish, King's College London. "Myosin cross-bridge dynamics in normal and diseased human myocardium"(2 years) £110,329

Dr G P McCann et al, University Hospitals of Leicester NHS. "Contribution of LVH and diastolic dysfunction assessed by myocardial tissue tagging to symptoms and exercise intolerance in severe aortic stenosis" (2 years) £149,583

Prof D A Middleton, University of Liverpool. "Mechanistic studies of the interaction between phosphorylated small molecules and phospholamban for the stimulation of cardiac relaxation" £54,273 (1 year)

Prof Sir G Radda CBE et al, University of Oxford. "Imaging metabolic rates in normal and diseased hearts using a novel MR technique" (2 years) £126,461

Dr A C Cave et al, King's College London "Mechanisms underlying the sustained cardiac troponin I phosphorylation in systemic sepsis" (3 years) £175,742

Prof A D Struthers et al, University of Dundee. "Do xanthine oxidase inhibitors reduce both left ventricular hypertrophy and vascular dysfunction in cardiovascular patients with renal dysfunction?" (2 years) £154,801

Prof M S Marber et al, King's College London. "Mechanism of myocardial p38-MAPK activation by ischaemia" (3 years) £193,652

Dr A Clerk & Prof P H Sugden, Imperial College London. "Regulation and function of activating transcription factor 3 (ATF3) in cardiac myocytes" (3 years) £194,417

Prof A H Baker & Dr S J George University of Glasgow. "Exploiting plaque-targeted adeno-associated viruses (AAV) to modify plaque biology in apoE-/- mice" (2 years) £112,342

Dr E P Morris & Prof J M Squire Institute of Cancer Research. "The structure and location of troponin in cardiac muscle thin filaments:implications for the molecular mechanism of Ca^{2+} regulation" (3 years) £137,039

Prof A B Parekh & Prof J C Ellory University of Oxford. "Function of STIM1 and Orai proteins in vascular endothelia" (2 years) £78,209

Prof L H Clapp & Prof M Singer, University College London. "Regulation of vascular K_{ATP} channels in sepsis" (3 years) £187,342

Dr A P Albert & Prof W A Large St Georges, University of London. "Study of the physiological functions of TRPC-mediated Ca^{2+} - permeable cation conductance in arterial smooth muscle cells" (3 years) £194,564

Dr I Khaliulin et al, University of Bristol. "The mechanism of temperature preconditioning and its relevance to cardioprotection during prolonged hypothermic ischaemia" (3 years) £211,375

Dr S J George et al, University of Bristol. "Reduction of plaque Instability by soluble N-cadherin" (3 years) £152,373

Dr T M Palmer, University of Glasgow. "Priming phosphorylated stat proteins for cytokine-triggered degradation in vascular endothelial cells: a new anti-inflammatory role for the A_{2A} adenosine receptor" (3 years) £165,545

PROJECT GRANTS COMMITTEE SEPTEMBER 2007

DEFERRED APPLICATIONS AWARDED

Prof L Smeeth et al, London School of Hygiene & Tropical Medicine. "Utilising randomised genetic variation in the innate immune response to investigate causality in the association between inflammation and cardiovascular disease" (3 years) £178,570

Dr J S Gibson, University of Cambridge. "Phosphatidylserine exposure in sickle cells" (3 years) £148,703

Prof M J Brown et al, University of Cambridge. "Hypertension due to Conn's adenoma - the localisation of adrenal cortical adenomas by ^{11}C-metomidate PET scanning following dexamethasone and fludrocortisone suppression" (3 years) £168,395

Dr D J Henderson, University of Newcastle. "Roles for Scrib in cardiomyocyte polarity" (3 years) £208,468

NEW APPLICATIONS AWARDED

Dr N Rabbani & Prof P J Thornalley, University of Warwick."Functional impairment of HDL by dicarbonyl glycation in glucose intolerance, obesity and type 2 diabetes - link to cardiovascular disease" (3 years) £250,477

Dr L Zeng & Prof Q Xu, King's College London. "The role of XBP1 in maintenance of endothelial cell integrity" (3 years) £164,597

Dr N D Jones & Prof K J Wood University of Oxford. "Identification of the mechanisms utilised by regulatory T cells to prevent T cell mediated rejection of heart allografts" (3 years) £161,892

Dr F M Marelli-Berg et al, Imperial College London. "Phosphoinositide 3-kinase p110δ as a pharmacological target to prevent T cell-mediated chronic rejection in heart transplant" (3 years) £208,241

Dr M Zaccolo, University of Glasgow. "Role of PDE2 in the control of cardiac myocyte hypertrophy" (3 years) £217,123

Dr C Denning et al, University of Nottingham. "A rational approach to improving and scaling production of human embryonic stem cell derived cardiomyocytes" (3 years) £165,834

Dr C Vial & Prof P Bradding, University of Leicester. "Identification and characterisation of human mast cell P2 receptors: study of their contribution to mast cell antithrombotic and proangiogenic activity" (3 years) £185,507

Prof E E Qwarnstrom & Dr E Kiss-Toth, University of Sheffield. "Control of bio-mechanical vascular cell responses through TILRR - a novel regulator of NF-kB" (3 years) £172,224

Dr M Peckham & Dr E White, University of Leeds. "The effects of cardiomyopathy-causing mutations in actin on contractile performance in rat adult cardiomyocytes" (2 years) £112,156

Prof M R Wilkins et al, Imperial College London. "Proteomic analysis of the pulmonary vasculature for informative biomarkers of pulmonary hypertension" (3 years) £238,246

Dr H Mellor, University of Bristol. "The role of endocytic trafficking of Src tyrosine kinase in VEGF signalling" (2 years) £114,082

Prof T D Warner & Prof J Mitchell Queen Mary, University of London. "Influences of nonsteroid anti-inflammatory drugs, including COX-2-selectives,on eicosanoid balance and platelet reactivity: roles for COX-1 and COX-2" (1.5 years) £65,327

Dr H K Graham et al, University of Manchester. "Adverse cardiac remodelling in heart disease and ageing: a role for the giant sarcomeric protein titin?" (3 years) £186,691

Dr S O Sage et al, University of Cambridge. "Molecular and functional characterisation of sodium-calcium exchangers and their role in secretion and calcium signalling in human platelets" (3 years) £71,110

Dr I M Fearon et al, University of Manchester. "Arrhythmogenic regulation of cardiac sodium channels: understanding the critical role of lysophosphatidylcholine in ischaemia" (2 years) £90,385

Prof J A Trinick & Prof S Homans, University of Leeds. "NMR spectroscopy studies of titin structure" (3 years) £190,243

Dr Y Senis et al, University of Birmingham. "Investigating the functional role of the platelet ITIM receptor G6b-B in thrombosis" (3 years) £150,776

FELLOWSHIPS COMMITTEE OCTOBER 2007

Intermediate Basic Science Research Fellowship

Dr V Sboros, University of Edinburgh. "Microbubble selective imaging for macro-, micro-vasculature and molecular targeting: a laboratory translational system" (4 years) £474,154

Dr J L Johnson, University of Bristol. "Do atherosclerotic plaques contain a distinct subpopulation of highly invasive and destructive foam cell macrophages?" (4 years) £365,386

4 Year PhD Studentship

Professor J Mullins, University of Edinburgh. Edinburgh 4th Intake 2007/2008 4 year PhD Studentships Scheme: Ms Rachel Dakin; Ms Louise Evans; Ms Sarah Robertson (4 years) £326,193

Professor J D Pearson, King's College London. King's College London 4th Intake 2007/2008 4 year PhD Studentship Scheme. Ms Jennifer Bodkin; Ms Anna Hsu; Ms Natasha-Jayne Hathaway (4 years), £351,381

Dr D R Greaves, University of Oxford. Oxford 4th Intake 2007/2008 4 year PhD Studentship Scheme: Ms Kiterie Faller; Ms Julie De Mesmaeker; Ms Jyoti Patel (4 years) £356,064

PhD Studentships

Unnamed and Prof C L Wainwright, Robert Gordon University, Aberdeen. "Studies to determine the cellular mechanisms of the anti-atherosclerotic effects of docohexaenoic acid - possible role for endocannabinoids" (3 years) £90,936

Mr W To, University of Birmingham. "A role for ATP in modulating vasomotion during hypoxia in umbilical cordblood vessels" (3 years) £89,839

Unnamed and Dr C Austin, University of Manchester. "Influence of PMCA4 ablation on vascular contractility" (3 years) £90,776

Unnamed and Prof S B Marston, Imperial College London. "Investigation of the molecular mechanism of familial dilated cardiomyopathy mutations in sarcomeric proteins" (3 years) £95,629

Mr D J Swan, University of Newcastle. "Modulation of immune response by Sphingosine-1- phosphate" (3 years) £87,332

Unnamed and Prof D Bates, University of Bristol. "Role of the endothelial glycocalyx in the regulation of vascular permeability" £91,535

Clinical Research Training Fellowship

Miss J M J Richards, University of Edinburgh. "Magnetic resonance imaging of abdominal aortic aneurysm instability" (3 years) £191,549

Dr A W Johnson, University of Oxford. "Metabolic control of energetics and efficiency in human heart: peroxisome proliferator activated receptors and uncoupling proteins" (3 years) £229,754

Dr P P Barman, University of Bristol. "Investigation of human atrial sodium calcium exchanger modulation and remodelling in atrial fibrillation" (3 years) £164,496

Cardiovascular Related Wellcome Trust Grants

Programme Grants

Professor Shoumo Bhattacharya, Wellcome Trust Centre For Human Genetics, University Of Oxford. Mechanisms Of Cardiovascular Pleiotropy And Buffering In Cited2 Deficiency. 60 Months £1,327,435

Professor David J Beech, Institute Of Membrane And Systems Biology, Garstang Building, Faculty Of Biological Sciences, University Of Leeds. Integrated Functions Of Trp Channels In Vascular Smooth Musccle Cells. 60 Months £1,111,396

Project Grants

Dr Colin Longstaff, National Institute For Biological Standards And Control, South Mimms. Cell Dependent Modulation Of Thrombolysis. 36 Months £184,844

Professor J R Arthur, The Rowett Research Institute, Bucksburn, Aberdeen. Interaction Of Se, Fatty Acids And A Polymorphism In GPX4 In Modulation Of Vascular Function. 36 Months £169,960

Professor Jonathan Flint, Wellcome Trust Centre For Human Genetics, Medical Sciences Division, University Of Oxford. Qtl Mapping Using A Rat Heterogeneous Stock. 36 Months £250,815

Professor Mauro Perretti, Department Of Biochemical Pharmacology, William Harvey Research Institute, Queen Mary, University Of London. Investigation On The Endogenous Annexin 1 System In Inflammatory Arthritis. 36 Months £278,080

Professor Dave Bates, Department Of Physiology, School Of Veterinary Sciences, University Of Bristol. Lymphatic Endothelial Mediated Cell Trafficking In Pathology. 24 Months £115,247

Dr Hannah Kuper, Department Of Infect And Tropical Diseases, London School Of Hygiene And Tropical Medicine. Nutritional Challenges, Abdominal Adiposity And Type 2 Diabetes In Indians. 30 Months £379,214

Professor Michael R Duchen, Department Of Physiology, University College London. The Role Of The Mitochondrial Endogenous Inhibitor, If-1, In Ischaemia And Reperfusion Injury In The Heart. 36 Months £277,607

Professor Philip N Baker, Maternal And Fetal Health, St Mary's Hospital, University Of Manchester. The Importance Of Endothelial Progenitor Cells In Intrauterine Growth Restriction. 36 Months £166,110

Equipment Grants

Dr Ian Marshall, School Of Clinical Science And Community Health, Medical Physics, University Of Edinburgh. High Frequency Ultrasound Scanner To Enable Real-Time, High Resolution Imaging For Biomedical Research. 60 Months £516,676

Professor Philip Blower, Division Of Imaging Sciences, School Of Medicine, King's College London. Small Animal PET Imaging For Translational Biomedical Research. 60 Months £977,082

University Award

Dr Mark J Paul-Clark, Department Of Cardiothoracic Pharmacology, Unit Of Critical Care Medicine, National Heart And Lung Institute. Role Of TLR2 In The Sensing Of Oxidants And Ensuing Inflammation: Implications For Therapeutic Intervention. 60 Months £429,836

Masters Fellowships In Public Health and Tropical Medicine

Dr Laura I Valencia, London School of Hygiene and Tropical Medicine. Physical Activity, Abdominal Obesity And Cardio-Metabolic Traits In An Urban Colombian Population. 30 Months £87,925

Ms Agnieszka Dorynska, Department Of Population Studies, Medical College, Jagiellonian University, Cracow Poland. Socioeconomic Determinants Of Disability In Eastern Europe. 30 Months £18,102

LATE SPRING MEETING 2008

A joint meeting with the

British Cardiovascular Society

"CAUSES AND CONSEQUENCES OF MYOCARDIAL INFARCTION: NEW CONCEPTS"

DATES: Monday 2nd and Tuesday 3rd June, 2008

VENUE: Manchester Central Convention Centre

STRUCTURE: The BSCR Spring Meeting will tale place over 1½ days in parallel with sessions held as part of the BCS Annual Scientific Meeting (2nd - 5th June). The BSCR dinner will be held on the evening of 2nd June.

PROGRAMME: The programme will consist of state-of-the-art presentations by leaders in the field and will include a keynote lecture and four symposia:

Unstable plaque: to inflammation and beyond

Targeting acute and chronic remodelling post-myocardial infarction

Electrophysiological consequences of myocardial ischaemia and remodelling

Novel developments in gene and cell therapy

Free Communications: Part of the programme will be devoted to oral presentation of selected abstracts and others will be presented in a poster exhibition. Submission of abstracts in any area of cardiovascular science is welcomed. There are two prizes of £250 each: the Clinical Science Early Investigator Award and the BSCR Early Investigator Award.

Student Bursaries: The BSCR will consider awarding travel grants of up to £200 to BSCR members who are bona fide students and application forms are available from the BSCR website (www.bscr.org).

Programme details, abstract pro-forma / guidelines, submission deadlines and registration / accommodation arrangements will be available for downloading from the BSCR website by the end of October 2007.

Further Information: Professor Barbara McDermott, BSCR Secretary: Email - b.mcdermott@qub.ac.uk; Phone - 02890 972242 / 975770;

Professor David Eisner, BSCR Chairman: Email - eisner@man.ac.uk; Phone - 0161 275 2702