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Editorial

Welcome to the October 2006 issue of *The* Bulletin!

This issue features a review article written by Dr Andrew James and colleagues at the University of Bristol. The authours provide a clear and fascinating overview of atrial fibrillation and remodelling, with insight into the value of various animal models and the potential for preventative therapeutic strategies.

As always, Professor Barbara McDermott has written an enjoyable Secretary's Column, highlighting the notable events and activities of the Society. Of particlar interest are details of recent and forthcoming BSCR meetings.

We are pleased to announce the winners of the Young Investigator prizes who presented their work at the recent meeting at Queen's College Cambridge; photographs of the winners receiving their prizes are shown in this issue. We will bring you further details and reports of the Autumn 2006 in the next issue of *The* Bulletin.

We're always delighted to include travel reports from readers of The Bulletin and this issue is no exception. Patricia Karjian reports back from a very dramatic Keystone Symposium. As well as the thrilling science, we hear how powerful snow storns and avalanches provided additional excitement!

Helen Maddock and Nicola Smart

Atrial fibrillation and atrial remodelling in heart disease: What insight from animal models?

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Atrial fibrillation (AF) is the most common arrhythmia and is associated with increased mortality, mainly due to its association with elevated risk of stroke. There are many predisposing risk factors for the development of AF, including valve diseases and congestive heart failure, and it is generally considered that AF is a progressive condition such that patients initially presenting with paroxysmal AF tend to progress to longer, non-self-terminating bouts of persistent or permanent AF. Intense research activity over the past decade, using both tissue samples from AF patients and various animal models, has established that electrical and structural changes to the atrial myocardium during AF, termed 'atrial remodelling,' play an important role in the stabilisation of the arrhythmia. However, the processes by which AF originates remain unclear. Recent data from animal models of heart disease indicate that atrial remodelling in these conditions makes the atrial myocardium more susceptible to atrial tachyarrhythmia, which may contribute to the increased risk of AF associated with heart disease. A fuller understanding of the processes occurring at the onset of AF may assist in the development of preventative therapeutic strategies for patients at increased risk of this condition.

Atrial fibrillation (AF) is a rapid and irregular activation of the atrial myocardium that results in a loss of co-ordinated atrial contraction. Since the atrial contribution to ventricular filling becomes particularly important at higher heart rates, from the perspective of the patient, the most obvious consequence is an impaired capacity for exercise. Perhaps more significantly, follow up of patients from the original Framingham heart study has revealed that AF is associated with an increased mortality, principally through an elevated risk of thrombo-embolic events and stroke due to pooling of blood within the atrial chambers (1-3), although uncontrolled ventricular rate in AF can also contribute to the development of heart failure (4). AF is the most common cardiac arrhythmia and accounts for more days of hospitalisation than the combined total of all ventricular arrhythmias; it therefore represents a significant economic burden on health service (3,4). The incidence of AF increases with age, being present in between 0.5% and 1% of the general population, rising to between 3% and 5% in those over 65 years of age and being almost 10% in octogenarians (1,3-5). The combination of these factors suggests that the socio-economic burden of this disease can be expected to increase with ageing of the population.

There are many possible causes of AF and the aetiology of the disease can be somewhat complex. Familial forms of AF involving gene mutations leading to 'channelopathies' to inward rectifier and slowed delayed rectifier K^+ currents (I_{K1} and I_{Ks} respectively) have been identified (6-8), but will not be considered in this review, which focuses on AF linked to heart disease. Indeed, in the vast majority of AF patients (~80%) there is some underlying heart disease (9-11). Epidemiological indicators that can be used to identify patients at risk of AF include, in addition to age and male gender, the presence of heart failure, ischaemic heart disease, myocardial infarction and hypertension (1-3,9). Furthermore, the existence of left ventricular dysfunction, left ventricular hypertrophy (LVH) and left atrial dilatation on echocardiography are strongly associated with AF (9,12-14). AF is a progressive condition; patients initially

presenting with paroxysmal AF tending to progress to longer, non-self-terminating bouts (3,4,9). Thus, it is in the interests of both patients and health services alike that effective therapeutic strategies be developed to, (i) prevent AF arising in at-risk patients, or (ii) maintain sinus rhythm in patients with early onset or paroxysmal AF and/or (iii) prevent the progression of paroxysmal AF to persistent and permanent forms. There has been much debate concerning the relative benefits and disadvantages in the management of AF of maintaining sinus rhythm (rhythm control) versus controlling the ventricular response (rate control) (e.g. (4,9,15,16)), which we do not intend to address here. Clearly, the development of therapeutic strategies to prevent the onset of AF and/or to block its progression to persistent and permanent forms necessitates a detailed understanding of the underlying processes. Animal models in which AF arising from a single cause can be studied in isolation represent an extremely valuable tool to this end (17).

Atrial fibrillation and re-entry

The predominant conceptual model for AF is that of multiple circuit re-entry, although rapid local ectopic activity and single circuit re-entry can also underlie the arrhythmia (extensively reviewed by Stanley Nattel and others; see (15,17-23)). Cardiac excitation can be thought of as an electrical wave, with the wavefront representing phase-0 depolarisation and the back of the wave being phase-3 repolarisation (23). The wavelength of excitation is then the product of the conduction velocity (CV) and the action potential duration (APD) (18,23). Re-entry can arise where heterogeneity in tissue structure (i.e. fibrosis, pectinate muscle inserts) and/or electrical properties (i.e. CV or APD) causes a break such that the wave rotates around and re-excites tissue that is no longer refractory (23). Thus, a key determinant of re-entry is the atrial effective refractory period (AERP); longer AERP make it more likely that a wave of electrical excitation will encounter tissue that remains refractory and so the arrhythmia will die out (18,23). It is thought that disease processes that increase heterogeneity in the structural and electrical properties of the atrial myocardium increase the likelihood that a trigger will result in a sustained fibrillation (18,23). However, the precise mechanisms underlying the genesis and maintenance of AF are still widely debated (e.g. (21,22)). For example, data from animal models of AF involving the experimental shortening of AERP through vagal or muscarinic stimulation provide evidence for single circuit re-entry or an ectopic focus (e.g. (24-30)). On the other hand, vagotonic forms of paroxysmal AF in patients are relatively uncommon (9,31) and it seems likely that distinct mechanisms of AF may be more common in other groups of patients (9,15). The atrial dilatation and enlargement, with interstitial fibrosis, of patients with heart disease is thought to favour multiple circuit re-entry (15,32).

Atrial remodelling and the stabilization of re-entry

Over the past decade, studies involving both tissue samples from patients and the use of animal models have provided considerable information concerning the processes underlying the stabilization of AF. It is clear from these studies that structural, electrical and contractile changes to the atrial myocardium during AF, termed atrial remodelling, make it more likely for the arrhythmia to be sustained (for reviews, see (17-20,33-35)). In patients with chronic AF, the AERP and APD become shortened and their adaptation to faster rates reduced (36-38). This electrical remodelling has been associated with changes in various ion current densities, including a reduction in the L-type Ca^{2+} current (I_{Ca}) and transient outward current (I_{to}) (36,38-41). However, reduction in I_{Ca} and I_{to} cannot account for the change in AERP and it has been suggested that increased outward current through inward rectifier K^+ channels plays a key role in the shortening of AERP in human AF (38,42-44). Conceivably, changes in the kinetics of the Na^+ current (*e.g.* recovery from inactivation) may also contribute to changes in AERP. A shift to depolarising potentials in the inactivation of the Na^+ current (I_{Na}) without any change in current density has been reported in atrial myocytes from patients with AF, suggesting altered Na^+ current kinetics in the remodelled atrium (36). It has been suggested that altered expression of the gap junction connexin proteins, Cx40 and Cx43, in AF may contribute to localized conduction abnormalities and perpetuation of re-entry (45-49). In addition, atrial dilatation and enlargement are thought to increase the likelihood of AF being maintained, presumably by increasing the available path-length for re-entry (18,23,33).

A highly influential proposal relating to AF is that atrial tachycardia itself produces electrical and structural remodelling of the atrium such that tachyarrhythmias and AF are more likely to be sustained (9,18,33). This may explain the progressive nature of the disease,

providing support for the proposal that 'AF begets AF' (50). Evidence for this came from studies of conscious goats in which rapid atrial pacing via implanted devices produced shortening of AERP and induced sustained episodes of AF (50,51). Chronic rapid pacing has also been shown to produce electrical remodelling of the atrium and increase susceptibility to sustained AF in the dog heart (52,53). Similar to the remodelling seen in atrial myocytes from AF patients, the electrical remodelling in the dog was associated with reduced I_{Ca} and I_{to} (54). On the other hand, in contrast to human AF, there was no change in the density of I_{K1} or Kir 2.1 mRNA expression in the canine model (54,55). In further contrast to results in AF patients, I_{Na} density was found to be reduced in the canine rapid pacing model of chronic AF and this reduction was associated with decreased expression of the Na^+ channel a-subunit (55,56). Thus, while the rapid atrial pacing models demonstrate that atrial tachycardia itself can lead to electrical remodelling, the changes in ion currents and channel expression underlying the electrical remodelling in these models are not necessarily representative of the changes occurring in patients with chronic AF, which itself is a multi-factorial pathology. In the rapid atrial pacing models, while AERP shortened within hours of commencing pacing, stabilisation of the AF took somewhat longer (weeks to months) and was associated with both structural and electrical remodelling involving atrial dilatation, interstitial fibrosis, changes in ion channel expression, localized slowing in conduction and changes in the distribution of gap junction proteins (50-53,55,57-64). Most significantly, the duration of sustained AF and the reversibility of this remodelling depended on the duration of the chronic rapid atrial pacing (50-52,59,65,66).

Atrial remodelling in animal models of heart disease.

An aspect of the pathogenesis of AF that is not reproduced by the rapid atrial pacing models is that AF most frequently occurs in association with some underlying heart disease. Evidence from animal models of congestive heart failure (CHF) and valve disease suggests that structural heart disease causes atrial remodelling that result in an electrical substrate for re-entry quite distinct from that produced by rapid atrial pacing. The atria from models of valve disease and heart failure show structural remodelling and dilatation (67-75). Studies conducted by Penelope Boyden and colleagues more than two decades ago have demonstrated increased susceptibility to atrial tachyarrhythmia (AT) in animals with structural heart disease (67-69). In a canine model of tricuspid insufficiency associated with right atrial enlargement, Boyden and colleagues showed that susceptibility to AT triggered by overdrive pacing in conscious animals was increased (67). A study of dogs with mitral valve fibrosis by the same group showed an increased incidence of both paroxysmal and chronic AF associated with left atrial enlargement and interstitial fibrosis (69). Note that in this case, the arrhythmias arose spontaneously without a requirement for an external trigger. Similarly, this group reported an increased incidence of AT and AF associated with left atrial enlargement and interstitial fibrosis in a study of cats with feline cardiomyopathy (68). However, although there was evidence of interstitial fibrosis in these studies, no measurements of AERP or conduction velocity were made and the nature of the arrhythmic substrate was unclear (67-69). A more recent study in a canine model of mitral valve regurgitation showed an increased susceptibility to AF triggered by overdrive pacing without reduction in ERP or WL (71). In fact, in this model, AERP was *increased* homogeneously throughout left and right atria (71). Importantly, there was evidence of markedly increased interstitial fibrosis in this model and mapping studies with an electrode array revealed localised conduction abnormalities (71,76). Similarly, a canine rapid ventricular pacing model of CHF also showed increased susceptibility to AF induced by overdrive pacing that was associated with atrial enlargement, interstitial fibrosis and localised conduction abnormalities (70). Again, the arrhythmic substrate in this model was *not* associated with shortening of atrial ERP or WL (70). In fact, AERP was slightly increased in some left atrial regions resulting in an increase in the regional heterogeneity in AERP (70). A goat model of atrial dilation associated with chronic atrioventricular block demonstrated an increased susceptibility to overdrive pacing-induced AF in which there were conduction abnormalities without any change in AERP (77). Intriguingly, despite the localised conduction slowing in this model, there was no evidence of fibrosis or changes in gap junction expression (77).

The most prevalent independent risk factor for AF is hypertension. It is striking, then, that there is very little information regarding atrial remodelling and susceptibility to AF from animal models of hypertension. We have conducted a study with a widely used model

of systemic hypertension, the spontaneously hypertensive rat (SHR), involving the comparison of susceptibility to burst-pacing-induced AT in excised, perfused hearts from SHR with hearts from their normotensive Wistar-Kyoto (WKY) controls at two ages (3 months and ~11 months; corresponding, respectively, to an early stage of hypertension and a pre-heart failure stage (78-80)). Hypertension was associated with significantly increased incidence and duration of AT and progressive interstitial fibrosis (81,82). A catheterization-based study of patients with CHF but without atrial arrhythmia is remarkably consistent with the suggestion from animal models that heart disease produces a form of remodelling distinct from that produced by AF itself, in that AERP was prolonged, and the atria of CHF patients showed localized conduction slowing and regions of electrical silence (83). A key point is that when AF occurs in a patient with heart disease it arises on the background of an atrial substrate conditioned by the pre-existing heart disease. Evidence from Nattel and colleagues' model of CHF suggests that the shortening of AERP and the electrical remodelling produced by atrial tachycardia (i.e. chronic rapid atrial pacing) is less pronounced in the setting of heart failure (84,85). On the other hand, AT-induced remodelling was not altered in the goat model of chronic atrial dilation (86). Thus, it appears that the nature of atrial remodelling depends on the underlying disease aetiology.

Atrial cellular electrical remodelling in heart disease

Although AERP has not been found to be shortened in models of heart disease, there is nevertheless evidence of remodelling of cellular electrophysiology. In their study of cats with feline cardiomyopathy, Boyden and colleagues showed significant changes in action potential properties (reduction in resting membrane potential, reduced phase 0 depolarisation velocity, depressed action potential amplitude) in isolated atrial tissue from enlarged atria (68). Interestingly, in this study, amongst the cats without atrial arrhythmia *per se*, there was an increased incidence of atrial premature depolarization associated with atrial remodelling, consistent with the contribution of abnormal automaticity or triggered activity to arrhythmogenesis (68). In Nattel and colleagues' canine rapid ventricular pacing model of CHF, left atrial $I_{Ca,L}$ and I_{to1} were reduced, presumably with reduction of repolarising I_{to1} and other repolarising currents (*i.e.* slow component of delayed rectifier, I_{Ks}) predominating since the normal rate-dependent adaptation of the atrial APD was attenuated such that the prolongation of APD at 90% repolarisation (APD_{90}) was most evident at *faster* heart rates (87). Notably, in marked contrast to rapid atrial pacing models of atrial electrical remodelling (54,55), the sodium-calcium exchange current ($I_{Na/Ca}$) was increased in this model of CHF (87). A role for remodelling of Na^+/Ca^{2+} exchange in AF associated with structural heart disease has been suggested by the up-regulation of exchanger protein expression (NCX1) in samples from mitral valve disease patients with AF as compared to those in sinus rhythm (88). Up-regulation of Na^+/Ca^{2+} exchange has been associated with ventricular arrhythmogenesis involving delayed afterdepolarisations and triggered activity in animal models of heart failure and hypertrophy (89-92). Further evidence for cellular electrical remodelling in atria in the setting of structural heart disease without AF includes reduced atrial $I_{Ca,L}$ in a rat model of CHF (93) and reduced atrial $I_{Ca,L}$, I_{to1} and $I_{K.ACh}$ in myocytes from dilated human right atria (94,95).

Mechanisms underlying development of the arrhythmic substrate in heart disease

Taken together, the evidence from animal models indicates that structural heart disease produces a substrate for AF such that, should a suitable trigger arise, an episode of AF is more likely to occur. Thus, an understanding of the mechansisms underlying atrial remodelling in heart disease (summarised in Fig. 1) may facilitate the development of therapeutic strategies for the prevention of AF (15). In congestive heart failure and mitral valve disease, it seems likely that pressure changes in the left atrium result in an increase in atrial wall stress that initiates remodelling (33,96). This remodelling may be maladaptive, as diastolic heart disease is associated with atrial contractile dysfunction that has itself been suggested to contribute to atrial dilatation (88,96-100). Moreover, left atrial contractile dysfunction is predictive of AF in patients with hypertrophic cardiomyopathy (13,14). Systemic hypertension also leads to increases in left atrial pressure, presumably as a result of the reduced left ventricular compliance and increased end diastolic pressure associated with left ventricular hypertrophy (96,101,102). Consistent with this suggestion, hypertrophic cardiomyopathy is itself a cause of AF (9,13,14). Certainly, models of hypertension associated with left ventricular hypertrophy demonstrate significant

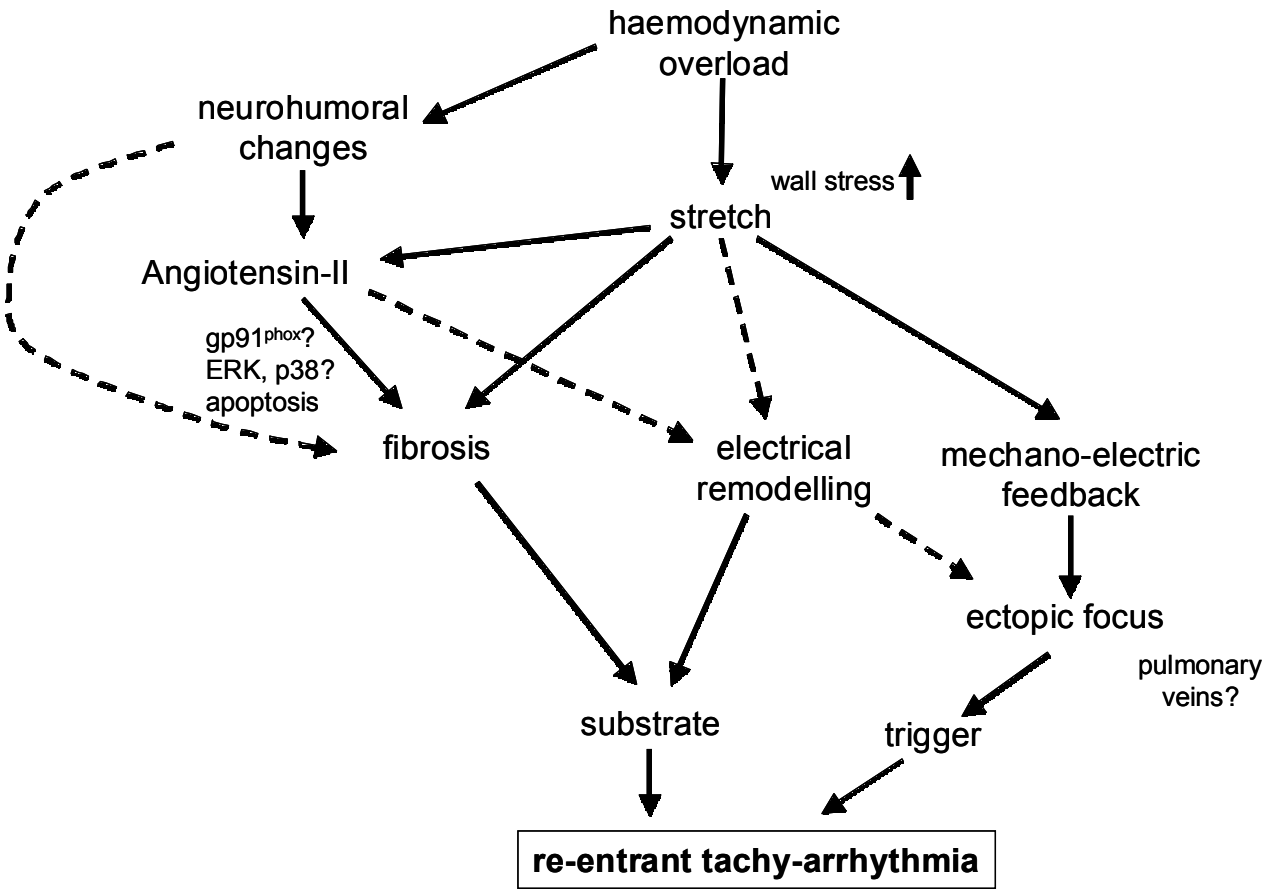

Figure 1. Flow diagram showing possible relationships between atrial remodelling and susceptibility to AF in heart disease. Dotted lines represent postulated links for which direct evidence is as yet not available.

atrial remodelling (72-74,103-105). As mentioned previously, the existence of left ventricular hypertrophy and left atrial enlargement in patients are epidemiological indicators of susceptibility to AF (9,12,106). Moreover, there is a correlation between arterial pressure and left atrial enlargement in hypertensive patients (107). However, the importance of atrial enlargement to the arrhythmic substrate *per se* may be open to question. The leading circle hypothesis of re-entry suggests that re-entry naturally establishes itself in a pathlength the size of the wavelength of excitation (18,108). It would therefore follow that atrial dilatation contributes to the arrhythmogenic substrate by providing a longer pathlength for re-entry. Concordant with this suggestion, in the canine model of mitral valve regurgitation, dogs with inducible sustained AF had more LA dilatation than dogs in which no episodes of AF could be induced (71). On the other hand, the appropriateness of the leading circle hypothesis for AF has been questioned since Na^+ channel blockers, that might be expected to promote arrhythmia through slowing of conduction velocity according to the leading circle hypothesis, are in fact very effective in the treatment of AF (18). Nevertheless, data from a number of reports support the notion of an association between AF and interstitial fibrosis and are consistent with localized conduction abnormalities contributing to an arrhythmic substrate in structural heart disease (67-71,76,109-111). It should be noted that it is possible that increases in intra-atrial pressure may acutely reduce AERP and/or elicit triggered activity through mechano-electrical feedback (112-114). Although most animal models of heart disease associated with changes in intra-atrial pressure do not show spontaneous AF, suggesting that the atrial pressure changes in heart disease may not be sufficient to trigger arrhythmia directly, mechano-electrical feedback may represent a trigger for episodes of AF where a suitable arrhythmic substrate has developed

through atrial remodelling (114).

Activation of the renin-angiotensin system (RAS) plays a central role in a number of cardiac disorders that themselves are risk factors for AF (115,116). Accumulating evidence indicates a role for the RAS in atrial remodelling of various causes (recently reviewed in (117)). The atria of AF patients express more angiotensin converting enzyme (ACE) and extracellular signal-related kinase (ERK) and show greater fibrosis than those of SR patients (118). There are also reports of changes in the density of AT_1 and AT_2 receptors, although there are apparently conflicting results from different groups (118,119). There is also evidence of apoptosis and increased caspase-3 expression in the atria of patients with AF or dilated atria (120). Angiotensin II (A-II), working through AT_1 receptors, stimulates myocyte hypertrophy and synthesis of collagen by cardiac fibroblasts, possibly through pathways involving $gp91^{phox}$ (121-124). A-II also couples to pathways involving MAP kinases such as ERK and p38 MAP kinase, respectively associated with hypertrophic cell growth and apoptosis (125). Data from canine models of atrial remodelling suggest the involvement of the RAS in both electrical and structural remodelling. The ACE inhibitor enalapril suppressed atrial fibrosis, reduced localized conduction defects, inhibited remodelling of gap junction proteins and attenuated susceptibility to AF in canine models of CHF (61,126-128). Nattel's group demonstrated significant apoptosis in the atrial myocardium within 24 hours of the onset of rapid ventricular pacing, which was preceded by increases in tissue (but not circulating) levels of A-II (126). Importantly, the increases in tissue A-II were inhibited and the apoptosis and fibrosis reduced, although not abolished, by enalapril treatment (126). The ARB candesartan prevented the acute shortening of atrial ERP produced by rapid atrial pacing for up to 3 hours in anaesthetised dogs, demonstrating a role for the RAS in the onset of electrical remodelling (60). Candesartan was also shown to inhibit the longer term structural remodelling induced by rapid atrial pacing (129). Thus, ACE inhibitors and AT_1 receptor antagonists may represent useful therapeutic agents for the prevention of AF in at-risk patients. Consistent with this suggestion, clinical trials have shown a reduced incidence of new onset AF in patients treated with ACE inhibitors (130-134) or AT_1 receptor blockers (ARB) (135,136). Inhibition of RAS may also facilitate the maintenance of sinus rhythm following electrical cardioversion (137,138).

Onset of AF

Comparatively little is known concerning the early onset of AF in heart disease. Factors considered to be responsible for the onset of AF include the triggers that induce the arrhythmia and the substrate by which the arrhythmia is sustained (9,23). Triggers might include atrial premature beats, tachycardia, accessory AV pathways, atrial stretch and sympathetic or parasympathetic stimulation (9). Paroxysms of AF in patients with structural heart disease most commonly occur in a setting of sympathetic stimulation (e.g. exercise, stress) (9,31). Studies within the last 10 years involving both patients and the use of animal models have revealed the importance of an ectopic focus associated with the junctions of the left atrium and the pulmonary veins in the initiation of paroxysms of AF (26,139-145). Numerous clinical investigators have demonstrated the importance of PV focal source ablation and/or PV-left atrial disconnection in the management of AF, confirming the role of this region in the initiation of atrial arrhythmia (139,140,146). There is evidence that autonomic denervation reduces the recurrence of AF in patients receiving PV ablation, indicating a role for innervation of the pulmonary vein in the genesis of AF (147). Numerous studies have demonstrated a role for triggered activity as a result of afterdepolarisations and/or abnormal automaticity in the generation of AF from the PVs, although re-entrant mechanisms may also contribute to the arrhythmogenesis (26,27,148-150). There is evidence that the junctions of the vena cavae with the right atrium may represent an alternative source of ectopic excitation (151,152) important in some patients with paroxysmal AF (139,140,153). Data from pulmonary vein preparations from animal models suggests that conditions associated with Ca^{2+} loading of the sarcoplasmic reticulum (i.e. rapid pacing, sympathetic or b-adrenergic stimulation) and shortening of the action potential (i.e. vagal or muscarinic stimulation) can predispose to triggered activity (154-160). There is also evidence from canine models that PVs are subject to electrical remodelling: Chronic rapid atrial pacing produces electrical remodelling of canine PV cardiomyocytes similar to that found in atrial myocytes; density of $I_{Ca,L}$ and I_{to1} is reduced and I_{K1} increased in remodelled cells (161,162). It can be expected that triggered activity would be enhanced by shortening of APD. The incidence of afterdepolarisations and spontaneous activity and the density of transient inward currents were markedly increased in canine PVs

following chronic rapid atrial pacing (161,163). Data from canine models suggest a role for ectopic foci in the pulmonary veins in the maintenance of AF in heart failure (144,164).

Summary

Data from animal models provide considerable insight into the mechanisms underlying the formation of the substrate for the origin of AF in various cardiac disorders. It is hoped that an improved understanding of the mechanisms underlying the origins of AF in heart disease will lead to the development of novel therapeutic strategies for the prevention of the arrhythmia in at-risk patients.

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References

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. *Circulation.* 1998;98:946-952.

2. Kannel WB, Wolf PA, Benjamin EJ, Levy D. *Am J Cardiol*. 1998;82:2N-9N.

3. Chugh SS, Blackshear JL, Shen W-K, Hammill SC, Gersh BJ. *J Am Coll Cardiol*. 2001;37:371-378.

4. Waktare JEP, Camm AJ. *Am J Cardiol*. 1998;81:3C-15C.

5. Hill JD, Mottram EM, Killeen PD. *J R Coll Gen Pract.* 1987;37:172-173.

6. Chen Y-H, Xu S-J, Bendahhou S, Wang X-L, Wang Y, Wen-Yuan X, Jin H-W, Sun H, Su X-Y, Zhuang Q-N, Yang Y-Q, Li Y-B, Liu Y, Xu H-J, Li X-F, Ma N, Mou C-P, Chen Z, Barhanin J, Huang W. *Science*. 2003;299:251-254.

7. Xia M, Jin Q, Bendahhou S, He Y, Larroque M-M, Chen Y, Zhou Q, Yang Y, Liu Y, Liu B, Zhu Q, Zhou Y, Lin J, Liang B, Li L, Dong X, Pan Z, Wang R, Wan H, Qiu W, Xu W, Eurlings P, Barhanin J, Chen Y. A *Biochem Biophys Res Comm*. 2005;332:1012-1019.

8. Yang Y, Xia M, Jin Q, Bendahhou S, Shi J, Chen Y, Liang B, Lin J, Liu Y, Liu B, Zhou Q, Zhang D, Wang R, Ma N, Su X, Niu K, Pei Y, Xu W, Chen Z, Wan H, Cui J, Barhanin J, Chen Y. *Am J Hum Genet.* 2004;75:899-905.

9. Allessie MA, Boyden PA, Camm AJ, Kleber AG, Lab MJ, Legato MJ, Rosen MR, Schwartz PJ, Spooner PM, Van Wagoner DR, Waldo AL. *Circulation*. 2001;103:769-777.

10. Lip GYH. *Atrial fibrillation in clinical practice*. 1st ed. London, UK: Martin Dunitz Ltd; 2001.

11. Murgatroyd FD, Camm AJ. *Lancet.* 1993;341:1317-1322.

12. Vaziri SM, Larson MG, Benjamin EJ, Levy D. *Circulation*. 1994;89:724-730.

13. Losi M-A, Betocchi S, Aversa M, Lombardi R, Miranda M, D'Alessandro G, Cacace A, Tocchetti C-G, Barbati G, Chiariello M. *Am J Cardiol*. 2004;94:895-900.

14. Tani T, Tanabe K, Ono M, Yamaguchi K, Okada M, Sumida T, Konda T, Fujii Y, Kawai J, Yagi T, Sato M, Ibuki M, Katayama M, Tamita K, Yamabe K, Yamamuro A, Nagai K, Shiratori K, Morioka S. *J Am Soc Echocard.* 2004;17:644-648.

15. Nattel S, Opie LH. *Lancet.* 2006;367:262-272.

16. Page RL, Roden DM. *Nat Rev Drug Discov.* 2005;4:899-910.

17. Nattel S, Shiroshita-Takeshita A, Brundel BJJM, Rivard L. *Prog Cardiovasc Dis*. 2005;48:9-28.

18. Nattel S. *Nature*. 2002;415:219-226.

19. Nattel S. *Cardiovasc Res*. 2002;54:347-360.

20. Nattel S, Li D, Yue L. *Ann Rev Physiol*. 2000;62:51-77.

21. Efimov IR, Fedorov VV. *Am J Physiol Heart Circ Physiol*. 2005;289:H977-H979.

22. Wu T-J, Kerwin WF, Hwang C, Peter CT, Chen P-S. *Heart Rhythm.* 2004;1:117-120.

23. Weiss JN, Qu Z, Chen P-S, Lin S-F, Karagueuzian HS, Hayashi H, Garfinkel A, Karma A. *Circulation*. 2005;112:1232-1240.

24. Allessie MA, Lammers WJ, Bonke IM, Hollen J. *Circulation.* 1984;70:123-135.

25. Liu L, Nattel S. *Am J Physiol.* 1997;273:H805-H816.

26. Mandapati R, Skanes A, Chen J, Berenfeld O, Jalife J. *Circulation.* 2000;101:194-199.

27. Mansour M, Mandapati R, Berenfeld O, Chen J, Samie FH, Jalife J. *Circulation.* 2001;103:2631-2636.

28. Kneller J, Zou R, Vigmond EJ, Wang Z, Leon LJ, Nattel S. *Circ Res.* 2002;90:73e-87.

29. Vigmond EJ, Tsoi V, Kuo S, Arevalo H, Kneller J, Nattel S, Trayanova N. *Heart Rhythm* 2004;1:334-344.

30. Zou R, Kneller J, Leon LJ, Nattel S. *Am J Physiol Heart Circ Physiol.* 2005;289:H1002-1012.

31. Coumel P. *J Cardiovasc Electrophysiol*. 1996;7:999-1007.

32. Mary-Rabine L, Albert A, Pham T, Hordof A, Fenoglio J, Jr, Malm J, Rosen M. *Circ Res*. 1983;52:188-199.

33. Allessie M, Ausma J, Schotten U. *Cardiovasc Res*. 2002;54:230-246.

34. Bosch RF, Nattel S. *Cardiovasc Res.* 2002;54:259-269.

35. Dobrev D, Ravens U. *Basic Res Cardiol*. 2003;98:137-148.

36. Bosch RF, Zeng X, Grammer JB, Popovic K, Mewis C, Kühlkamp V. *Cardiovasc Res*. 1999;44:121-131.

37. Franz MR, Karasik PL, Li C, Moubarak J, Chavez M. *J Am Coll Cardiol.* 1997;30:1785-1792.

38. Workman AJ, Kane KA, Rankin AC. *Cardiovasc Res.* 2001;52:226-235.

39. Christ T, Boknik P, Wohrl S, Wettwer E, Graf EM, Bosch RF, Knaut M, Schmitz W, Ravens U, Dobrev D. *Circulation*. 2004;110:2651-2657.

40. van Wagoner DR, Pond AL, Lamorgese M, Rossie SS, McCarthy PM, Nerbonne JM. *Circ Res.* 1999;85:428-436.

41. van Wagoner DR, Pond AL, McCarthy PM, Trimmer JS, Nerbonne JM. *Circ Res*. 1997;80:772-781.

42. Dobrev D, Friedrich A, Voigt N, Jost N, Wettwer E, Christ T, Knaut M, Ravens U. *Circulation*. 2005;112:3697-3706.

43. Dobrev D, Graf E, Wettwer E, Himmel HM, Hala O, Doerfel C, Christ T, Schuler S, Ravens U. *Circulation*. 2001;104:2551-2557.

44. Zhang H, Garratt CJ, Zhu J, Holden AV. *Cardiovasc Res.* 2005;66:493-502.

45. Kanagaratnam P, Cherian A, Stanbridge RD, Glenville B, Severs NJ, Peters NS. *J Cardiovasc Electrophysiol*. 2004;15:206-216.

46. Kostin S, Klein G, Szalay Z, Hein S, Bauer EP, Schaper J. *Cardiovasc Res*. 2002;54:361-379.

47. Polontchouk L, Haefliger J-A, Ebelt B, Schaefer T, Stuhlmann D, Mehlhorn U, Kuhn-Regnier F, De Vivie ER, Dhein S. *J Am Coll Cardiol.* 2001;38:883-891.

48. Severs NJ, Dupont E, Coppen SR, Halliday D, Inett E, Baylis D, Rothery S. *Biochim Biophys Acta*. 2004;1662:138-148.

49. Wetzel U, Boldt A, Lauschke J, Weigl J, Schirdewahn P, Dorszewski A, Doll N, Hindricks G, Dhein S, Kottkamp H. *Heart*. 2005;91:166-170.

50. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA. *Circulation*. 1995;92:1954-1968.

51. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Power J, Allessie MA. *Circulation*. 1997;96:3710-3720.

52. Gaspo R, Bosch RF, Talajic M, Nattel S. *Circulation*. 1997;96:4027-4035.

53. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. *Circulation*. 1995;91:1588-1595.

54. Yue L, Feng J, Gaspo R, Li G-R, Wang Z, Nattel S. *Circ Res.* 1997;81:512-525.

55. Yue L, Melnyk P, Gaspo R, Wang Z, Nattel S. *Circ Res*. 1999;84:776-784.

56. Gaspo R, Bosch RF, Bou-Abboud E, Nattel S. *Circ Res*. 1997;81:1045-1052.

57. Ausma J, Wijffels M, Thone F, Wouters L, Allessie M, Borgers M. *Circulation*. 1997;96:3157-3163.

58. Everett TH, IV, Li H, Mangrum JM, McRury ID, Mitchell MA, Redick JA, Haines DE. *Circulation*. 2000;102:1454-1460.

59. Fareh S, Villemaire C, Nattel S. *Circulation*. 1998;98:2202-2209.

60. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. *Circulation*. 2000;101:2612-2617.

61. Sakabe M, Fujiki A, Nishida K, Sugao M, Nagasawa H, Tsuneda T, Mizumaki K, Inoue H. *J Cardiovasc Pharmacol*. 2004;43:851-859.

62. van der Velden HMW, Ausma J, Rook MB, Hellemons AJCGM, van Veen TAAB, Allessie MA, Jongsma HJ. *Cardiovasc Res*. 2000;46:476-486.

63. van der Velden HMW, Zee L, Wijffels MCEF, Leuven C, Dorland R, Vos MA, Jongsma HJ, Allessie MA. *J Cardiovasc Electrophysiol.* 2000;11:1262-1269.

64. Ausma J, Litjens N, Lenders M-H, Duimel H, Mast F, Wouters L, Ramaekers F, Allessie M, Borgers M. *J Mol Cell Cardiol.* 2001;33:2083-2094.

65. Elvan A, Wylie K, Zipes DP. *Circulation.* 1996;94:2953-2960.

66. Garratt CJ, Duytschaever M, Killian M, Dorland R, Mast F, Allessie MA. *J Cardiovasc Electrophysiol.* 1999;10:1101-1108.

67. Boyden PA, Hoffman BF. *Circ Res*. 1981;49:1319-1331.

68. Boyden PA, Tilley LP, Albala A, Liu SK, Fenoglio Jr JJ, Wit AL. *Circulation.* 1984;69:1036-1047.

69. Boyden PA, Tilley LP, Pham TD, Liu SK, Fenoglic Jr JJ, Wit AL. *Am J Cardiol.* 1982;49:1896-1908.

70. Li D, Fareh S, Leung TK, Nattel S. *Circulation.* 1999;100:87-95.

71. Verheule S, Wilson E, Everett T, IV, Shanbhag S, Golden C, Olgin J. *Circulation.* 2003;107:2615-2622.

72. Wang X, Gerdes AM. *J Mol Cell Cardiol*. 1999;31:333-343.

73. Wang X, Li F, Campbell SE, Gerdes AM. *J Mol Cell Cardiol* 1999;31:319-331.

74. Wang X, Li F, Gerdes AM. *J Mol Cell Cardiol*. 1999;31:307-317.

75. Boixel C, Fontaine V, Rucker-Martin C, Milliez P, Louedec L, Michel J-B, Jacob M-P, Hatem SN. *J Am Coll Cardiol*. 2003;42:336-344.

76. Verheule S, Wilson E, Banthia S, Everett TH, IV, Shanbhag S, Sih HJ, Olgin J. *Am J Physiol*. 2004;287:H634-H644.

77. Neuberger H-R, Schotten U, Verheule S, Eijsbouts S, Blaauw Y, van Hunnik A, Allessie M. *Circulation*. 2005;111:30-37.

78. Pfeffer JM, Pfeffer MA, Fishbein MC, Frohlich ED. *Am J Physiol.* 1979;237:H461-H468.

79. Conrad CH, Brooks WW, Robinson KG, Bing OHL. *Am J Physiol.* 1991;260:H136-H145.

80. Bing OHL, Brooks WW, Robinson KG, Slawsky MT, Hayes JA, Litwin SE, Sen S, Conrad CH. *J Mol Cell Cardiol*. 1995;27:383-396.

81. Choisy SCM, Arberry LA, Jones JV, Hancox JC, James AF. *J Mol Cell Cardiol*. 2005;39:196.

82. Choisy SCM, Arberry LA, Vann Jones J, Hancox JC, James AF. *Biophys J*. 2006;90:545A.

83. Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK,

Sparks PB, Kalman JM. *Circulation*. 2003;108:1461-1468.

84. Cha T-J, Ehrlich JR, Zhang L, Nattel S. *Circulation*. 2004;110:1520-1526.

85. Shinagawa K, Li D, Leung TK, Nattel S. *Circulation*. 2002;105:251-257.

86. Neuberger H-R, Schotten U, Blaauw Y, Vollmann D, Eijsbouts S, van Hunnik A, Allessie M. *J Am Coll Cardiol*. 2006;47:644-653.

87. Li D, Melnyk P, Feng J, Wang Z, Petrecca K, Shrier A, Nattel S. *Circulation.* 2000;101:2631-2638.

88. Schotten U, Greiser M, Benke D, Buerkel K, Ehrenteidt B, Stellbrink C, Vazquez-Jimenez JF, Schoendube F, Hanrath P, Allessie M. *Cardiovasc Res.* 2002;53:192-201.

89. Pogwizd SM, Bers DM. *Trends Cardiovasc Med.* 2004;14:61-66.

90. Pogwizd SM, Qi M, Yuan W, Samarel AM, Bers DM. *Circ Res.* 1999;85:1009-1019.

91. Pogwizd SM, Schlotthauer K, Li L, Yuan W, Bers DM. *Circ Res.* 2001;88:1159-1167.

92. Meszaros J, Khananshvili D, Hart G. *Am J Physiol*. 2001;281:H903-H914.

93. Boixel C, Gonzalez W, Louedec L, Hatem SN. *Circ Res.* 2001;89:607-613.

94. Le Grand B, Hatem S, Deroubaix E, Couetil J-P, Coraboeuf E. *Cardiovasc Res*. 1994;28:548-556.

95. Koumi S, Arentzen C, Backer C, Wasserstrom J. *Circulation.* 1994;90:2213-2224.

96. Mandinov L, Eberli FR, Seiler C, Hess OM. *Cardiovasc Res.* 2000;45:813-825.

97. Schotten U, de Haan S, Neuberger H-R, Eijsbouts S, Blaauw Y, Tieleman R, Allessie M. *Am J Physiol.* 2004;287:H2324-H2331.

98. Schotten U, Duytschaever M, Ausma J, Eijsbouts S, Neuberger H-R, Allessie M. *Circulation*. 2003;107:1433-1439.

99. Schotten U, Neuberger H-R, Allessie MA. *Prog Biophys Mol Biol*. 2003;82:151-162.

100. Sachdev V, Shizukuda Y, Brenneman CL, Birdsall CW, Waclawiw MA, Arai AE, Mohiddin SA, Tripodi D, Fananapazir L, Plehn JF. *Am Heart J.* 2005;149:730-736.

101. Noresson E, Rickstein S-E, Thoren P. *Acta Physiol Scand.* 1979;107:9-12.

102. Noresson E, Ricksten S-E, Hallback-Nordlander M, Thoren P. *Acta Physiol Scand*. 1979;107:1-8.

103. Joseph J, Washington A, Joseph L, Kennedy RH. *Clinical and Experimental Pharmacology and Physiology*. 2004;31:331-337.

104. Okazaki H, Minamino T, Tsukamoto O, Kim J, Okada K-i, Myoishi M, Wakeno M, Takashima S, Mochizuki N, Kitakaze M. *Hypertens Res*. 2006;29:277-284.

105. Zhang C, Yasuno S, Kuwahara K, Zankov DP, Kobori A, Makiyama T, Horie M. *Circ J*. 2006;70:335-341.

106. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. *J Am Med Assoc*. 1994;271:840-844.

107. Vaziri SM, Larson MG, Lauer MS, Benjamin EJ, Levy D. *Hypertens.* 1995;25:1155-1160.

108. Allessie MA, Bonke FI, Schopman FJ. *Circ Res.* 1977;41:9-18.

109. Hayashi H, Omichi C, Miyauchi Y, Mandel WJ, Lin S-F, Chen P-S, Karagueuzian HS. *Am J Physiol*. 2003;285:H2091-H2098.

110. Hayashi H, Wang C, Miyauchi Y, Omichi C, Pak HN, Zhou S, Ohara T, Mandel WJ, Lin SF, Fishbein MC, Chen PS, Karagueuzian HS. *J Cardiovasc Electrophysiol*. 2002;13:801-808.

111. Verheule S, Sato T, Everett T, IV, Engle SK, Otten D, Rubart-von der Lohe M, Nakajima HO, Nakajima H, Field LJ, Olgin JE. *Circ Res*. 2004;94:1458-1465.

112. Babuty D, Lab M. *J Cardiovasc Electrophysiol*. 2001;12:323-329.

113. Ravelli F, Allessie M. *Circulation*. 1997;96:1686-1695.

114. Ravelli F. *Prog Biophys Mol Biol.* 2003;82:137-149.

115. Sigurdsson A, Swedberg K. *Am Heart J.* 1996;132:229-234.

116. Unger T. *Am J Cardiol.* 2002;89:3-9.

117. Healey JS, Morillo CA, Connolly SJ. *Curr Opin Cardiol*. 2005;20:31-37.

118. Goette A, Staack T, Rocken C, Arndt M, Geller JC, Huth C, Ansorge S, Klein HU, Lendeckel U. *J Am Coll Cardiol*. 2000;35:1669-1677.

119. Boldt A, Wetzel U, Weigl J, Garbade J, Lauschke J, Hindricks G, Kottkamp H, Gummert JF, Dhein S. *J Am Coll Cardiol.* 2003;42:1785-1792.

120. Aime-Sempe C, Folliguet T, Rucker-Martin C, Krajewska M, Krajewski S, Heimburger M, Aubier M, Mercadier J-J, Reed JC, Hatem SN. *J Am Coll Cardiol.* 1999;34:1577-1586.

121. Byrne JA, Grieve DJ, Bendall JK, Li J-M, Gove C, Lambeth JD, Cave AC, Shah AM. *Circ Res*. 2003;93:802-805.

122. Li J-M, Shah AM. *Am J Physiol*. 2004;287:R1014-R1030.

123. Brilla CG, Zhou G, Matsubara L, Weber KT. *J Mol Cell Cardiol.* 1994;26:809-820.

124. Sadoshima J-I, Izumo S. *Circ Res*. 1993;73:413-423.

125. Dorn II GW, Brown JH. *Trends Cardiovasc Med.* 1999;9:26-34.

126. Cardin S, Li D, Thorin-Trescases N, Leung T-K, Thorin E, Nattel S. *Cardiovasc Res.* 2003;60:315-325.

127. Li D, Shinagawa K, Pang L, Leung TK, Cardin S, Wang Z, Nattel S. *Circulation*. 2001;104:2608-2614.

128. Shi Y, Li D, Tardif J-C, Nattel S. *Cardiovasc Res*. 2002;54:456-461.

129. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K,

Saku K. *J Am Coll Cardiol*. 2003;41:2197-2204.

130. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmaki K, Dahlof B, de Faire U, Morlin C. *Lancet*. 1999;353:611-616.

131. L'Allier PL, Ducharme A, Keller P-F, Yu H, Guertin M-C, Tardif J-C. *J Am Coll Cardiol*. 2004;44:159-164.

132. Pedersen OD, Bagger H, Kober L, Torp-Pedersen C. *Circulation*. 1999;100:376-380.

133. Pizzetti F, Turazza FM, Franzosi MG, Barlera S, Ledda A, Maggioni AP, Santoro L, Tognoni G. *Heart*. 2001;86:527-532.

134. Vermes E, Tardif J-C, Bourassa MG, Racine N, Levesque S, White M, Guerra PG, Ducharme A. *Circulation*. 2003;107:2926-2931.

135. Maggioni AP, Latini R, Carson PE, Singh SN, Barlera S, Glazer R, Masson S, Cere E, Tognoni G, Cohn JN. *Am Heart J*. 2005;149:548-557.

136. Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlof B, Ibsen H, Julius S, Kjeldsen SE, Lindholm LH. *J Am Coll Cardiol*. 2005;45:712-719.

137. Madrid AH, Bueno MG, Rebollo JMG, Marin I, Pena G, Bernal E, Rodriguez A, Cano L, Cano JM, Cabeza P, Moro C. *Circulation*. 2002;106:331-336.

138. Ueng K-C, Tsai T-P, Yu W-C, Tsai C-F, Lin M-C, Chan K-C, Chen C-Y, Wu D-J, Lin C-S, Chen S-A. *Eur Heart J*. 2003;24:2090-2098.

139. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. *N Engl J Med*. 1998;339:659-666.

140. Chen S-A, Hsieh M-H, Tai C-T, Tsai C-F, Prakash VS, Yu W-C, Hsu T-L, Ding Y-A, Chang M-S. *Circulation*. 1999;100:1879-1886.

141. Zhou S, Chang C-M, Wu T-J, Miyauchi Y, Okuyama Y, Park AM, Hamabe A, Omichi C, Hayashi H, Brodsky LA, Mandel WJ, Ting C-T, Fishbein MC, Karagueuzian HS, Chen P-S. *Am J Physiol*. 2002;283:H1244-H1252.

142. Arora R, Verheule S, Scott L, Navarrete A, Katari V, Wilson E, Vaz D, Olgin JE. *Circulation*. 2003;107:1816-1821.

143. Kalifa J, Jalife J, Zaitsev AV, Bagwe S, Warren M, Moreno J, Berenfeld O, Nattel S. *Circulation*. 2003;108:668-671.

144. Okuyama Y, Miyauchi Y, Park AM, Hamabe A, Zhou S, Hayashi H, Miyauchi M, Omichi C, Pak H-N, Brodsky LA. *J Am Coll Cardiol*. 2003;42:348-360.

145. Wu T-J, Ong JJC, Chang C-M, Doshi RN, Yashima M, Huang H-LA, Fishbein MC, Ting C-T, Karagueuzian HS, Chen P-S. *Circulation*. 2001;103:1157-1163.

146. Nattel S. *Heart Rhythm*. 2005;2:1346.

147. Pappone C, Santinelli V, Manguso F, Vicedomini G, Gugliotta F, Augello G, Mazzone P, Tortoriello V, Landoni G, Zangrillo A, Lang C, Tomita T, Mesas C, Mastella E, Alfieri O. *Circulation*. 2004;109:327-334.

148. Chen Y-J, Chen S-A. *J Cardiovasc Electrophysiol*. 2006;17:220-224.

149. Hocini M, Ho SY, Kawara T, Linnenbank AC, Potse M, Shah D, Jais P, Janse MJ, Haissaguerre M, de Bakker JMT. *Circulation*. 2002;105:2442-2448.

150. Nattel S. *J Cardiovasc Electrophysiol*. 2003;14:1372-1375.

151. Rozanski GJ, Lipsius SL. *Am J Physiol*. 1985;249:H594-603.

152. Rubenstein D, Lipsius S. *Circ Res*. 1989;64:648-657.

153. Chen S-A, Tai C-T. *J Cardiovasc Electrophysiol*. 2005;16:229-232.

154. Cheung DW. *J Physiol (Lond)*. 1981;314:445-456.

155. Cheung DW. *Nature*. 1981;294:582-584.

156. Honjo H, Boyett MR, Niwa R, Inada S, Yamamoto M, Mitsui K, Horiuchi T, Shibata N, Kamiya K, Kodama I. *Circulation*. 2003;107:1937-1943.

157. Miyauchi Y, Fishbein MC, Karagueuzian HS. *Am J Physiol*. 2004;287:H178-H186.

158. Miyauchi Y, Hayashi H, Miyauchi M, Okuyama Y, Mandel WJ, Chen P-S, Karagueuzian HS. *Heart Rhythm*. 2005;2:1339-1345.

159. Patterson E, Lazzara R, Szabo B, Liu H, Tang D, Li Y-H, Scherlag BJ, Po SS. *J Am Coll Cardiol*. 2006;47:1196-1206.

160. Patterson E, Po SS, Scherlag BJ, Lazzara R. *Heart Rhythm*. 2005;2:624-631.

161. Chen Y-J, Chen S-A, Chen Y-C, Yeh H-I, Chan P, Chang M-S, Lin C-I. *Circulation*. 2001;104:2849-2854.

162. Cha T-J, Ehrlich JR, Zhang L, Chartier D, Leung TK, Nattel S. *Circulation*. 2005;111:728-735.

163. Chen Y-J, Chen S-A, Chang M-S, Lin C-I. *Cardiovasc Res*. 2000;48:265-273.

164. Ryu K, Shroff SC, Sahadevan J, Martovitz NL, Khrestian CM, Stambler BS. *J Cardiovasc Electrophysiol*. 2005;16:1348-1358.

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PRIZES AWARDED AT THE AUTUMN 2006 JOINT BSCR/BAS MEETING

Once again, ***Clinical Science*** have generously sponsored a Young Research Worker's Prize, which was won by Ziad Ali (Wellcome Trust Centre for Human Genetics, University of Oxford) for his presentation entitled 'Tetrahydrobiopterin-dependent eNOS coupling mediates endothelial regeneration and attenuates vein graft atherosclerosis in apoE-KO mice.'

Dr Ziad Ali receives the Clinical Science Prize from Dr Chris Newman (BAS/BSCR)

The BSCR Prize was won by Andrew Bond of Imperial College, London for his presentation on 'Variation in blood flow patterns around arterial branches with age.'

BSCR Secretary, Professor Barbara McDermott presents the BSCR Prize to Andrew Bond

Secretary's Column

The Autumn 'gathering' held at Queen's College, Cambridge, was a first for the BSCR and the British Atherosclerosis Society, who joined forces to put on an amazingly concentrated programme on 'Biomechanical signalling in atherosclerosis'. The organizers, Dorian Haskard and Peter Weinberg from Imperial College, and Quigbo Xu from St George's Hospital did a fine job in delivering a meeting that both enlightened and entertained. Highlight of the social programme was a formal dinner in the Old Hall, which captivated both local delegates and speakers from further afield, as did the post dinner menu of organ recital in the chapel or drinks in the College bar. Most opted for both. Wonderfully orchestrated by Natasha Dougall from Weldon Events, she distributed 'happy' sheets and got best agreement for 'The meeting was worth the time I invested in it', which says a lot. Also, I would like to mention appreciation of Chris Newman's input who, wearing both BAS and BSCR hats, steered an amiable course through the early organizational negotiations, ending up with an agreed aspiration to hold further joint meetings.

Because of the expanded programme lasting two full days, the Committee met the previous evening and what is usually a two hour meeting extended to just over four hours. It is probably true to say that the generous allocation of wine with supper contributed to lively discussion. My problem now is to write the minutes of the meeting from a selection of random notes. I have, however, managed to extract a few points of general interest. Firstly, may I remind members to look at the BSCR website for information about forthcoming meetings, for which full details are usually available about six months in advance, often before they appear in this Bulletin. Other features include the immediate posting of winners of the Young Investigator prizes at each meeting. Also, please note the section for advertising job or study opportunities and if you wish to use this facility, send the details to chris.jackson@bristol.ac.uk. A topic which warranted lengthy deliberation in committee was the possibility of the BSCR choosing to hold its Spring meeting within the British Cardiovascular Society meeting, usually held in May/June. Despite some practical and financial issues, there is general support for the idea and more detailed consideration will take place with a view to putting a programme in place for 2008.

In the meantime, arrangements for BSCR activities in early 2007 are well advanced. Katrina Bicknell and Gavin Brooks are hosting the Spring meeting at the University of Reading at the end of March. Details are advertised in this issue of the Bulletin, and forms for abstract submission and registration etc. are available on the website. The BSCR along with other BCS affiliate groups put forward three symposia and a teach-in session for possible inclusion in the BCS annual meeting to be held in Glasgow in early June 2007. Thanks to those of you who responded to the request for proposals, all of which were viewed favourably and have been included in the final programme. Titles of the symposia are 'Vascular calcification', 'Endothelial dysfunction and thrombosis following stent insertion' and 'Cardiovascular adverse drug reactions', and the teach-in addresses the question 'Is the failing heart in need of more energy'? It is encouraging to be able to make such a significant contribution to the BCS scientific programme and this hopefully will provide an extra incentive for BSCR members to submit abstracts for the free communication sessions.

And finally, are there any ideas out there for BSCR workshop meetings along with willing organizers? The Society can help with advertising and contribution to costs. Our suggestion for a topic which is timely, likely to be of significant interest and has potential for drug company sponsorship is '*In vivo* pharmacology'. I look forward to hearing from you about this or with other offers.

Barbara McDermott

BSCR Spring Meeting 2007- Provisional Programme

Emerging Therapeutic Targets and Technologies for the Treatment of Cardiovascular Disease

Dates: 29-30th March, 2007

Venue: School of Pharmacy, University of Reading

Organisers: Dr Katrina Bicknell and Prof. Gavin Brooks

The theme of the meeting will focus on the identification of novel therapeutic targets for the treatment of cardiovascular disease and the development of new technologies for the delivery of therapeutic agents to the cardiovascular system. Topics presented will include the identification and evaluation of novel drug targets, novel delivery methods, such as gene therapy approaches and/or drug-eluting stents, tissue engineering and cell-based therapies.

DAY 1 (THURSDAY 29TH MARCH)

12:30 – 1:50 Registration and Buffet Lunch
1:50 – 2:00 Welcome and Introduction

Session 1: Identification of Novel Therapeutic Targets

2:00-2:30 Prof. Mike Dunn (Dublin)
Cardiovascular proteomics for the identification of novel biomarkers and therapeutic targets for cardiovascular disease

2:30-3:00 Dr Manuel Mayr (St Georges)
Combining proteomics and metabolomics to identify novel therapeutic targets the treatment of cardiovascular disease

3:00-3:30 Prof. Steve Humphries (UCL)
Pharmacogenetics: clinical potential for coronary heart disease

3:30-4:00 Dr Clive Long (Organon Laboratories)
From small molecules to drug discovery: targeting the cardiovascular system

4:00-4:30 TEA

Session 2: Keynote Lecture

4:30-5:30 Prof. Rudiger von Harsdorf (Toronto, Canada)
Novel therapeutic targets for myocardial repair and protection

Session 3: Posters

5:30-7:00 Posters and Wine Reception

7:30 - Conference Dinner (Wantage Hall, University of Reading)

DAY 2 (FRIDAY 30TH MARCH 2007)

Session 4: Novel therapies and delivery methods targeting the vasculature

9:00-9:30 Prof Jon Gibbins (Reading)
Identification of drug targets for the prevention and treatment of thrombosis
9:30-10:00 Prof. Andrew Baker (Glasgow)
Gene delivery methods for the vasculature
10:00-10:30 Dr. Martin Oberhoff (Bristol)
Drug-eluting stents: Advances in the prevention of restenosis
10:30-11:00 Prof. Noel Caplice (Cork)
Cell-based therapy for the induction of therapeutic angiogenesis

11:00-11:30 TEA

Session 5: Free Communications from selected abstracts

11:30-11:45
11:45-12:00
12:00-12:15
12:15-12:30

12:30-1:30 LUNCH

Session 6: Novel therapies and drug delivery for the diseased myocardium
1:30-2:00 Dr Andrew Trafford (Manchester)
Targeting sarcoplasmic reticulum function for the treatment of cardiovascular disease
2:00-2:30 Dr Huseyin Ince (Rostock, Germany)
Cytokine therapy for cardiac protection and repair.
2:30-3:00 Dr Pat Taylor (NHLI, London)
Therapeutic potential of tissue engineering heart valves

3:00-3:30 TEA

Session 7: Keynote Lecture

3:30-4:30 To Be Confirmed

4:30-4:45 Prize giving and Meeting close

BSCR Travel Report

Keystone Symposium: Snowbird, Utah, April 2006

"Metabolomics - From Bioenergetics to Apoptosis"

Written by Patricia Karjian

Physiology and Clinical Interventions Applied Research Group
Faculty of Health and Life Sciences, Coventry University

Set nestled in the Wasatch Mountain range in Utah, the Keystone Symposia meeting brought together 270 scientists from academia, government and industry to discuss the bioenergetic status of a cell and its role in determining a cell's susceptibility to apoptosis. As an avid skier I was thrilled at the idea of spending a week at Snowbird Resort, considered one of the top ski resorts in the United States. With much gratitude to the organizers of the meeting, between seminars and poster sessions, a block of time every afternoon had been set aside for activities. The clear blue skies and powder perfect "dry" Utah snow, however, lasted only one day. Here we were discussing the "powerhouse" of the cell, the mitochondria, while the skies above us unleashed their own power in four straight days of what was the biggest storm Utah had seen all year! Organized trips to explore Park City, home to the 2002 Winter Olympics, and Salt Lake City still provided fun trips away from the mountain storms.

Skiing at 11,000 feet elevation, Mount Superior in the distance

The central focus of the meeting was on mitochondrial function and apoptosis, the contribution of metabolic regulators and the role of bioenergetic sensing pathways. Although this meeting centered on understanding the pathogenesis and improving the treatment of many diseases, this report will primarily highlight those pertaining to the cardiovascular system.

The keynote address, given by Dr. Douglas Wallace from UC-Irvine, was an excellent start to the meeting which he began with the philosophic words of Descartes, "I think therefore I am", bringing relevance to a much deeper cellular level. He also brought to light the idea of mtDNA polymorphisms in the shifting of mitochondrial energy allocation based on different climatic surroundings. For instance, humans that have migrated from tropical Africa to arctic Siberia will have a shift in mitochondrial energy allocation from a predominant production of ATP to more heat generation.

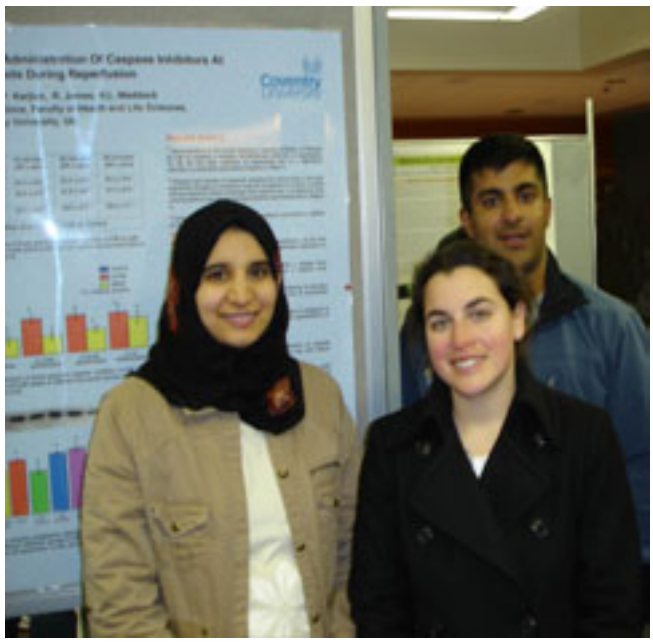
Dr. Martin Crompton from University College London gave an interesting lecture addressing whether the mitochondria permeability transition pore (mPTP) is also involved in the apoptotic cell death that accompanies necrosis. This research demonstrated that permeability transition (PT) is not involved in ischemia/reperfusion (I/R)-induced apoptosis and that the PT is a strictly necrotic mechanism. By monitoring the translocation of Bax to the mitochondria the initiation of apoptosis in I/R was investigated proving that apoptosis begins in the ischemic period but requires early reperfusion to avoid PT and necrosis.

Stunning reflections in the conference center building

One day of lectures was dedicated to oxidative stress regulation and cell death. Research conducted at Northwestern University by Dr. Navdeep Chandel looked at the regulation of apoptosis and gene expression during hypoxia by the mitochondrial electron transport. Past research has shown that the ability of the cells to undergo apoptosis during anoxia depends on the activation of Bax or Bak but this work provided evidence that individual loss of upstream regulators of Bax or Bak, namely Bim, Bid, Puma, Noxa, Caspase-2 and HIF-1β do not prevent anoxia-induced cell death. However, the loss of Mcl-1 is triggered by anoxia independent of Bax or Bak. Therefore, the activation of the Bax/Bak dependent cell death during anoxia depends on the cooperation of loss of Mcl-1 protein and the inhibition of the mitochondrial electron transport chain.

Dr. Paul Brooks from the University of Rochester presented his work on nitric oxide (NO) as a critical regulator of mitochondrial function in hypoxia/ischemia. This research proposes that nitric oxide inhibition is cardioprotective in the setting of ischemia-reperfusion injury. Previous work in this lab has shown that mitochondrial s-nitrosation occurs during the cardioprotective setting of ischemic preconditioning. They have developed a series of mitochondrially targeted NO donors which have shown potent cardioprotection in both isolated cardiomyocytes and perfused heart models of IR injury. During these studies they stumbled upon some interesting findings in regards to langendorff perfusion studies. They have found that the recovery of an ischemic rat heart is light sensitive and presented significant data comparing the % Recovery RPP between an ischemic heart in darkness and light. Current research is now being conducted to find out which wavelength of light is affecting the heart and building light shielding chambers.

Similar topics on nitric oxide in poster presentation showed research that NO can mediate both pro- and anti-oxidant effects through the regulation of transcriptional co-activator PGC-1α. Other research demonstrated PCG-1α, and regulation by NO, is involved in specific and coordinated regulation of the mitochondrial system. Continued studies are now aimed at identifying specific transcription factors that interact with PGC-1α to regulate the mitochondrial ROS protection system.



Our group's poster presentation

As part of Coventry University's cardiovascular research group we presented two posters at the conference. One focused on the reduction of myocardial injury by administration of caspase inhibitors at time points during reperfusion and the other presented our research on A3 adenosine receptor activation in protecting the myocardium via anti-apoptotic and pro-survival pathways.

Another poster in the cardiovascular arena showed research that identified anaerobic electron flux through the electron transport chain as a novel mechanism of acquired ischemic tolerance that is induced by the cellular oxygen sensor. These studies have concluded that prolyl hydroxylase inhibitors (PHIs)

and their activation of proline hydroxylase-domain containing enzymes (PHD) oxygen-sensing mechanism lead to multiple compensatory changes in cardiomyocytes which lead to robust cytoprotection against metabolic insult.

As the conference came to a close we prepared for the much anticipated planned finale entertainment but the storm only progressed. Not only was the entertainment cancelled but we were forced into lock-down in our hotel for the next 16 hours where food supplies were diminished and the roads were closed. We listened to endless hours of triggered avalanches as missiles were fired

Warning sign posted in our hotel

and grenades dropped by helicopter. In an attempt to catch our early morning flight, my colleague and I jumped at the opportunity that night to drive down to the city when the roads were briefly opened. We were stopped short in our tracks when, seconds before us, a car was toppled and engulfed by an avalanche that left a family of seven hanging, suspended by their seat-belts, until rescue crews could save them. Abandoning our cars we were transported back to the hotel where lock-down resumed and a lobby of upset scientists all missed their morning flights. We received thirty inches of snow in just one day.

This conference provided an interesting and enlightening look at apoptosis and the function of the mitochondria. Expecting to see a lot of breakthrough research and fascinating studies, I had not anticipated the type of adrenaline rush I encountered. Be prepared for what you might be getting yourself into at the next scientific conference!

The remnants of the storm

Travel Reports for *The* Bulletin

The Bulletin editors look forward to publishing travel reports written by BSCR members. These can be on any conference, course or laboratory visit of interest to other members and could perhaps contain photographs. If you are planning to travel to a cardiovascular-related meeting and would like to write a report for the Bulletin, please contact the editors. A bursary of **£300** is available towards the cost of your visit, and this will be provided on receipt of the report. *Bon voyage!*

Cardiovascular Related Meetings

British Congenital Cardiac Association, 22 November 2006 To 23 November 2006. The Assembly Rooms, Bath. For further information, contact Mrs Christine MacFadden, Cardiac Secretary; Tel: 0117 342 8854; E-mail: Christine.MacFadden@ubht.nhs.uk; Website: www.congenitalheart.co.uk/welcome.htm

Euroecho 10 The Tenth Annual Meeting of the European Association of Echocardiography in cooperation with the Working Group on Echocardiography of the Czech Society of Cardiology, 6th-9th December, 2006. Prague, Czech Republic. Contact Details: EUROECHO 10 Secretariat, Tel: +33 (0)4 92 94 76 00; E-mail: euroecho@escardio.org; Website: www.escardio.org/congresses/EE/EE10/.

Keystone Symposia: "Moleular Pathways in Cardiac Development and Disease" and "Integrative Basis of Cardiovascular Disease", Breckenridge, Colorado, 22nd-27th January, 2007. Further information is available: www.keystonesymposia.org; E-mail: info@keystonesymposia.org; Tel: (800) 253-0685 or (970) 262-1230

Hands-on Course in Cardiac Morphology, 26-27 February 2007, National Heart & Lung Institute, London SW3 6LY. Further details may be obtained from: Academic Events Office; Tel: 020 7351 8172; E-mail: academicevents.nhli@imperial.ac.uk. Website: www1.imperial.ac.uk/medicine/about/divisions/nhli/events/

Keystone Symposia: "Molecular Mechanisms of Fibrosis: From Bench to Bedside", Granlibakken Resort, Tahoe City, California, 11-15th March 2007. Further information: www.keystonesymposia.org; E-mail: info@keystonesymposia.org; Tel: (800) 253-0685 or (970) 262-1230

Keystone Symposia: "Metabolic Syndrome and Cardiovascular Risk", Sheraton Steamboat Resort, Steamboat Springs, Colorado. 27th March-1st April, 2007. For further information: www.keystonesymposia.org; E-mail: info@keystonesymposia.org; Tel: (800) 253-0685 or (970) 262-1230

76th European Atherosclerosis Society Congress, 10-13 June 2007. Helsinki, Finland. For further information: Tel: +41 22 908 0488; E-mail: eas2007@kenes.com; Website: www.kenes.com/eas2007

XIX ISHR World Congress in Bologna, Italy **22-26 June 2007**. Organizers Roberto Ferrari and Luigi Tavazzi. **Enquiries:** Prof. Roberto Ferrari, Chief of Cardiology, University Hospital of Ferrara, Corso Giovecca 203, 44100 Ferrara, Italy. E-mail: info@ishr-italy2007.org, Website www.ishr-italy2007.org

4th European Meeting on Vascular Biology and Medicine, University of Bristol, 17th-20th September, 2007. Visit the website: www.emvbm.org for refular meeting updates. Secretariat: Wheldon Events & Conferences. Tel:+44 (0)1922 457984; Fax:+44 (0)1922 455238; E-mail: info@wheldonevents.freeserve.co.uk.

British Heart Foundation Grants

May 2006 to October 2006

Project Grants
Deferred Applications Awarded

Prof H S Markus & Dr S N Bevan St Georges, University of London. "Genetic variation in the leukotriene pathway as a risk factor for atherosclerosis". 1 year, £63,022

Dr A R Bushell & Prof K J Wood University of Oxford. "Exploitation of bystander regulation to protect heart transplants from rejection: a novel mechanism for the generation of regulatory T cells". 3 years £156,726,

Dr G R Barclay et al, University of Edinburgh. "Preclinical in vivo evaluation of potential sources of human endothelial progenitor cells for autograft cellular therapy of ischaemia". 3 years, £239,930

Dr T J A Chico et al, Northern General Hospital, Sheffield. "Using the zebrafish to determine the genetic control of arteriogenesis". 3 years, £178,973

Prof D F Goldspink et al., Liverpool John Moores University. "An integrative study of the effects of controlled exercise intensity on overall cardiac function and adaptations at the level of the cardiomyocyte". 3 years, £202,081

Prof J A Mitchell & Prof T D Warner, Imperial College London. "Understanding the relative role of the nuclear receptor PPAR α versus prostacyclin (IP) receptor in the anti-platelet effects of prostacyclin". 2 years, £104,876

Dr M El Mezgueldi & Prof S B Marston, University of Leicester. "Effects of dilated and hypertrophic cardiomyopathy mutations in cardiac muscle troponin and tropomyosin on the dynamics of the Ca^{2+}-regulatory mechanism". 3 years, £123,116

New Applications Awarded

Dr J S Mitcheson & Prof A B Tobin, University of Leicester. "G-protein coupled receptor modulation of HERG potassium channels in cardiac myocytes". 2 years, £146,188

Dr I A Greenwood, St Georges, University of London. "Functional impact and molecular identity of KCNQ and ERG channels in the murine vasculature". 3 years, £173,789

Prof R J Plevin, University of Strathclyde.. "The regulation of endothelial cell apoptosis by MAP kinase phosphatase-2 - towards a possible clinical application". 2 years, £112,128

Dr P W F Hadoke et al, University of Edinburgh. "11α-hydroxysteroid dehydrogenases and vascular remodelling after tissue injury". 2 years, £145,808

Dr D A Giussani, University of Cambridge. "Developmental programming of cardiovascular disease by hypoxia and oxidative stress". 3 years, £170,497

Mr R S Bonser et al, University of Birmingham. "The effects of tri-iodothyronine and methylprednisolone on the suitability of donor hearts for transplantation". 1.5 years, £88,619

Dr J A Ellis, King's College London. "An investigation into how defects in the protein emerin result in the cardiac dysrhythmias observed in X-linked Emery-Dreifuss muscular dystrophy patients". 3 years, £149,885

Dr P M Bennett & Dr J C Fordham, King's College London. "3D ultrastructure of the transitional region between myofibril and intercalated disc in normal and DCM heart". 3 years, £209,421

Dr W S V Ho et al, University of Nottingham. "Role of endogenous cannabinoids in the regulation of vascular tone". 2 years, £31,433

Dr A J T George, Imperial College London. "Endothelial expression of indoleamine 2,3-dioxygenase and its role in controlling inflammation". 3 years, £133,100

Prof S P Newman et al, University College London. "Psychological response and impact of an ICD on quality of life in young and older recipients for primaryprevention". 3 years, £113,722

Dr P D Taylor et al, King's College London. "The role of leptin in hypothalamic programming of offspring appetite and raised blood pressure by maternal obesity". 3 years, £223,665

Dr A Ferro et al, King's College London. "Mechanisms underlying the dependence on extracellular L-arginine of calcium-independent activation of endothelial nitric oxide synthase". 3 years, £165,755

Dr J Wells et al, University College London (ICH). "Validation of bioelectrical impedance analysis across ethnic groups in adolescents". 1 year, £35,708

Prof T N Dear, University of Sheffield. "Genetic mapping and phenotypic characterisation of the mouse mutant Phar Lap". 2 years, £110,119

Dr E Poschl, University of East Anglia. "Characterisation of isolated murine pericytes and their role in angiogenesis" 3 years, £172,821

Dr G F Baxter, The Royal Veterinary College, London. "Role of Rho-dependent kinase in mediating reperfusion injury". 3 years, £156,609

Dr J Li & Dr S M O Hourani et al, University of Surrey. "Cross-talk between adenosine 2A receptor and angiotensin II receptors in coronary microvascular endothelial cells: the role of NADPH oxidase". 3 years, £143,547

Dr G Lombardi et al, King's College London. "Preclinical study of tolerogenic dendritic cells as cell therapy to induce donor-specific heart transplantaion tolerance using murine and human SCID mouse models". 3 years, £191,236

Prof S Bhattacharya, University of Oxford. " Control of ventricular topology by Nodal and Cited2". 3 years, £250,203

Prof N M Hooper et al, University of Leeds. "Genetic and molecular regulation of angiotensin converting enzyme-2 (ACE2)". 2 years, £90,834

Prof A S Ahmed & Dr P W Hewett, University of Birmingham."Differential signalling of the vascular endothelial growth factor receptors in angiogenesis". 2 years, £119,809

Prof D J Paterson, University of Oxford. "Gene transfer strategy to modulate cardiac sympathetic and beta adrenergic hyperactivity in hypertension". 3 years, £197,679

Dr S Sultan et al, King's College London. "Rapid priming of endothelial cell functional responses by cytokines and growth factors". 3 years, £168,084

Dr Z L S Brookes & Prof N Brown, University of Sheffield "Ang-1 modulates sepsis-induced microvascular responses". 3 years, £166,253

Dr P D Taylor et al, King's College London. "Developmental programming of cardiac dysfunction by maternal overnutrition in pregnancy". 3 years, £180,588

Dr A J Jovanovic, University Of Dundee. "Non-channel aspects of sarcolemmal K_{ATP} channels and cardioprotection". 3 years, £154,293

Dr P Garside et al, University of Strathclyde. "Investigating the role of T cells in vascular pathology". 3 years, £232,467

Project Grants

Dr A E Pickering & Prof J F R Paton, University of Bristol. "Role of preganglionic neurones in controlling the respiratory modulation of sympathetic activity: a possible pathogenic locus in hypertension". 3 years, £181,590

Dr S Kasparov & Prof J F R Paton, University of Bristol. "Is junctional adhesion molecule-1 expression in the brainstem pro-hypertensive?". 3 years, £158,180

Prof A C Newby & Mr G J Murphy, University of Bristol. "Towards effective inhibition of neointima formation in saphenous vein grafts". 2 years, £108,485

Prof P Collins et al, Imperial College London. "Cardiac rehabilitation for the treatment of refractory angina". 2 years, £141,407

Prof G Y H Lip et al, University of Birmingham. "Biomarkers in the prediction of heart failure and prognosis in South Asian subjects in the community". 2 years, £216,674

Dr R A S Ariens et al, University of Leeds. "Heterogeneity of plasmin inhibitor: origin, distribution, and implications for cross-linking to fibrin and fibrinolytic potential". 3 years, £137,381

Prof K J Broadley et al, Cardiff University. "Trace amines in the regulation of vascular tone". 2 years, £95,863

Dr P A Kingston, University of Manchester. "Optimisation of promoters for therapeutic transgene expression in vascular smooth muscle cells". 3 years, £182,622

Dr R L Riha et al, University of Edinburgh. "Aortic distensibility in the obstructive sleep apnoea syndrome using cardiovascular MRI and pulse wave analysis: effect of CPAP therapy". 2 years, £162,200

Dr A Clerk, Imperial College London. "Signalling to transcription and translation in cardiac myocyte growth and death". 2 years, £49,894

Dr Y Jamshidi et al, St Georges, University of London. "Genetic and environmental contribution to QT interval duration in the normal population: a UK twin candidate gene study". 2 years, £113,095

Dr G E Rainger et al, University of Birmingham. "The role of platelets adherent to endothelial cells in promoting leukocyte recruitment in flow-based models of arterial disease". 2 years, £87,385

Prof P Madeddu et al, University of Bristol. "Resident progenitor cells in adult human arteries and veins: isolation, characterisation and contribution to post-natal vascular regeneration". 3 years, £156,894

Dr M Tomaszewski et al, University of Leicester. "The Y chromosome and cardiovascular disease - an evolving understanding of the molecular mechanisms". 2 years, £111,653

Dr G C Burdge et al, University of Southampton. "Effect of nutrition before and after birth on fat metabolism and function in the adult heart". 2 years, £89,958

Prof M P Frenneaux et al, University of Birmingham. "Pathophysiology of heart failure with preserved left ventricular ejection fraction". 2 years, £64,500

Dr T J Mohun National Institute for Medical Research. "Identifying target genes of the cardiac transcription factor Nkx2-5". 3 years, £174,215

Prof M R Bennett et al, University of Cambridge. "The regulation of ARC, a myocyte specific anti-apoptotic protein". 3 years, £191,555

Dr L Zhao et al, Imperial College London. "Pharmacological treatment with tetrahydrobiopterin in pulmonary hypertension". 3 years, £163,162

Dr J Y Jeremy et al, University of Bristol. "Mechanisms underlying the inhibition of superoxide formation by hydrogen sulfide in vascular cells: impact on replication, migration and angiogenesis". 2 years, £103,478

Prof M P Frenneaux et al, University of Birmingham. "Mechanisms responsible for cardiac and skeletal muscle energetic impairment in type 1 diabetes". 2.5 years, £199,887

Prof M P Frenneaux et al, University of Birmingham. "Modification of myocardial substrate utilisation as a therapy for heart failure". 2 years, £234,607

Prof J E Sanderson et al, Keele University. "Understanding 'diastolic' heart failure: what is the role of impaired ventricular long axis function and torsion?". 3 years, £256,681

Prof M T Kearney et al, University of Leeds. "Exploring the role of insulin-like growth factor binding protein-2 in protecting against the development of obesity". 3 years, £161,237

Dr G Manoharan & Prof J Adgey, Royal Victoria Hospital, Belfast. "Defibrillation of ventricular fibrillation using novel shock waveforms". 2 years, £86,672

Prof S Bhattacharya & Dr J Bentham, University of Oxford. "Interactions between maternal diabetes and genetic risk in cardiac malformation". 3 years, £148,516

Mr W A Owens & Dr N Hole, University of Durham. "The use of telomerase as a functional marker of native cardiac stem cells in health and disease". 3 years, £132,809

Dr M A Laffan & Prof A Dell, Imperial College London. "The role of N-linked glycosylation in von Willebrand factor structure and function". 3 years, £146,351

Dr D J Grieve et al, Queen's, University, Belfast. "Role of NADPH oxidase-derived reactive oxygen species in cardiac dysfunction associated with doxorubicin chemotherapy". 3 years, £170,952

Dr P R Riley, University College London. "Investigating the role of Prox1 during vertebrate heart development". 3 years, £237,329

Intermediate Research Fellowships

Dr S T Yao, University of Bristol. "Neural changes contributing to autonomic dysfunction following chronic heart failure". 3 years, £135,016

Dr S Muzaffar, University of Bristol. "The interactive role of NADPH oxidase, superoxide and phosphodiesterases in mediating the replication and migration of vascular cells". 3 years, £118,279

Dr N Balthasar, University of Bristol. "Identifying key neuronal pathways mediating melanocortin's cardiovascular effects". 3 years, £163,229

Clinical PhD Studentships

Mr G Morris, University of Manchester. "Gene

expression in the pacemaker of the heart, the sinoatrial node". 3 years, £153,543

Mr S Chaubey, King's College London. Mechanisms of Nox2 NADPH oxidase-dependent interstitial fibrosis in the hypertensive heart". 3 years, £186,340

Senior Research Fellowship

Dr B Casadei, University of Oxford. "RENEWAL: Role of myocardial reactive oxygen species in the onset and maintenance of atrial fibrillation". 5 years, £614,483

Clinical Research Training Fellowship

Dr A K Reed, Imperial College London. "Role of prostacyclin IP and PPARα receptors in pulmonary hypertension". 3years, £174,630

Dr F C Connell, St Georges, University of London. "Systematic investigation of patients with primary lymphoedema". 2 years, £112,609

Dr A G Japp, University of Edinburgh. "The cardiovascular effects of apelin *in vivo* in man". 2 years, £112,327

Non-Clinical PhD Studentship

Unnamed and Dr G Blanco, MRC Mammalian Genetics Unit,Didcot. "Functional characterization and disease evaluation of KYIP1, a novel heart and skeletal muscle cytoskeletal protein". 3 years, £79,874

Ms N Marshall, King's College London. "Does the TRPV1 receptor play a role in maintaining vasodilator tone?". 3 years, £ 94,381

Miss L Copland, University of Strathclyde. "The role of calcium/calmodulin dependent protein kinase II in modulation of NF-kappa B signaling in normal and hypertrophied hearts". 3 years, £77,887

Miss A Geraghty, University of Manchester. "Functional role and regulation of the Ca^{2+}-sensing and related receptors in blood vessels". 3 years, £83,984

Mr B Maddox, University of Cambridge. "Investigation of von Willebrand factor-binding sites in collagen. 3 years, £91,803

Unnamed and Dr M A Laffan, Imperial College London. "A comprehensive glycan map of von Willebrand factor". 3 years, £91,348

Unnamed and Dr V Ohanian, University of Manchester. "The role of adducin in vascular smooth muscle". 3 years, £86,948

Marian and Christina Ionescu Fellowship

Dr N M Bittar, "LVAD fellowship". 2 years, £26,152

Dr A Bagga, Glenfield Hospital, Leicester. "The role of protein kinases in ischaemic and pharmacological preconditioning in human myocardium: sequence of activation and effect of age". 2 years, £ 97,150

Programme Grants

Prof DA Eisner & Dr S C O'Neill, University of Manchester. "The role of dyssynchronized Ca release in calcium alternans and its relationship to electrical alternans". 5 years, £586,024

Prof I C Zachary & Prof J F Martin, University College London. "Mechanisms mediating VEGF regulation of endothelial function in cultured cells and in vivo: roles of signalling, gene regulation and neuropilin" 5 years (renewal: years 6-10) £862,745

Prof M L Rose & Dr A Chester, Imperial College London. "Effect of the indirect alloimmune response on microvascular endothelial cells and protection by hsp27" 5 years (renewal: years 16-20) £804,077

Submission Deadlines for *The* Bulletin:

Volume	*Date*	*Deadline*
20 (1)	***January 2007***	*1st Dec*
20 (2)	***April 2007***	*1st March*
20 (3)	***July 2007***	*1st June*
20 (4)	***October 2007***	*1st September*

Cardiovascular Related Wellcome Trust Grants

May 2006 to October 2006

Wellcome Trust Centre Grants

Professor Anthony P Monaco, Wellcome Trust Centre For Human Genetics, University Of Oxford, Headington. Identification And Functional Analysis Of Susceptibility Genes In Multifactoral Disease24 Months, £4,184,432

Professor Martin J Humphries, Faculty Of Life Sciences, University Of Manchester, Michael Smith Building, Manchester. Renewal Of Core Support For The Wellcome Trust Centre For Cell-Matrix Research. 24 Months, £929,747

Hcpc Phd Fellowship

Mr Gerry H Mshana, Department Of Anthropology, , University Of Durham, Durham. Perceptions And Treatment Seeking For Stroke In Rural And Urban Tanzania. 24 Months, £26,226

Research Career Development Fellowship

Dr N M Morton, Endocrinology Unit, Department Of Medical Sciences, University Of Edinburgh, Western Gen, Edinburgh. Investigating Genetic Leanness: What Goes "Right" In Obesity-Resistance. 48 Months, £473,300

Project Grants

Professor David J Webb, Clinical Pharmacology Unit, Western General Hospital, University Of Edinburgh. Reno-Selective Nitric Oxide Donor Drugs: Preliminary Toxicology And Metabolism Studies. 6 Months, £58,750

Professor Michael J Shipston, Department Of Biomedical Sciences, Membrane Biology Group, University Of Edinburgh. Role Of A Cysteine Rich Domain In Hypoxia Sensing Of Calcium-Activated Potassium Channels. 36 Months, £262,239

Dr Kim A Dora, Department Of Pharmacy And Pharmacology, University Of Bath. Investigation Of The Mechanisms Integrating Endothelial Cell Calcium With Myogenic Reactivity In Resistance Arteries. 36 Months, £305,339

Dr John H Walker, Endothelial Cell Biology Unit, Institute Of Molecular And Cellular Biology, University Of Leeds. Cytosolic Phospholipase A2α Association With The Golgi Apparatus Regulates Vascular Function. 36 Months, £156,624

Programme Grants

Professor David A Leon, Department Of Epidemiology And Pop Health, Epidemiology Unit, London School Of Hygiene And Tropical Medicine. Alcohol And Mortality: From Aetiology To Intervention. 48 Months, £878,568

Professor Martin J Prince, Section Of Epidemiology And Gen Pract, , Institute Of Psychiatry, London. Cardiovascular Risk, Nutrition And Dementia Incidence In Admixed Populations Undergoing Rapid Health Transition - Latin America And China. 54 Months, £1,478,019

Professor Elizabeth M C Fisher, Department Of Neurodegenerative Disease, Nat Hospital Of Neurology And Neurosurgery, University College London. A Genetic Dissection Of Brain And Heart Phenotypes In The Tc1 Transchromosomic Mouse Model Of Down Syndrome. 60 Months, £606,749

Professor Jane A Mitchell. Cardiothoracic Pharmacology, Imperial College London, National Heart And Lung Institute London. Role Of Cox-1 And Cox-2 In The Cardiovascular System: Relevance To Understanding The Side Effects Of Nsaids Including Cox-2 Selective Inhibitors. 18 Months £123,871

Strategic Translation Award

Professor Brian R Walker, Endocrinology Unit, Department Of Medical Sciences, University Of Edinburgh, Western Gen, Edinburgh. 11 Beta-Hydroxysteroid Dehydrogenase Type 1 Inhibition: Tissue-Specific Control Of Cortisol Action In Neurological, Metabolic And Cardiovascular Disease. 24 Months, £1,894,016

University Translation Award

Dr Andrew Gee Department Of Engineering, , University Of Cambridge Cambridge. Clinically Practical Two-And Three-Dimensional Ultrasonic Elasticity Imaging. 36 Months, £213,508

Equipment Grants

Dr Kevin M Brindle, Department Of Biochemistry, University Of Cambridge. A 500 Mhz NMR Spectrometer For High-Throughput Metabolomics To Examine Multi-Factorial Diseases In Mammalian Systems. 36 Months, £220,367

Dr Richard F Mott, Wellcome Trust Centre For Human Genetics, University Of Oxford. Large Scale Data Storage And Backup Strategy For The Wellcome Trust Centre For Human Genetics For The Period 2006-2010. 60 Months, £195,129

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)

Visit the new and improved BSCR Website:

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BSCR Spring Meeting 2007

EMERGING THERAPEUTIC TARGETS AND TECHNOLOGIES FOR THE TREATMENT OF CARDIOVASCULAR DISEASE

Dates: Thursday 29th and Friday 30th March, 2007

Venue: Palmer Building, Whiteknights Campus, University of Reading, UK

Organisers: Dr Katrina Bicknell and Professor Gavin Brooks

Objectives: The principal objective of the meeting is to highlight state-of-the-art research that focuses on the identification of novel therapeutic targets for the treatment of cardiovascular disease and the development of new technologies for the delivery of therapeutic agents to the cardiovascular system. Topics will include the identification and evaluation of novel drug targets, novel drug or gene delivery methods, tissue engineering and cell-based therapies.

Programme: The programme will consist of state-of-the-art presentations by leaders in the field. Speakers will include: Mike Dunn (Dublin), Manuel Mayr (London), Steve Humphries (London), Clive Long (Newhouse, Scotland), Rudi von Harsdorf (Toronto), Jon Gibbins (Reading), Andrew Baker (Glasgow), Martin Oberhoff (Bristol), Noel Caplice (Cork), Andrew Trafford (Manchester), Huseyin Ince (Rostock, Germany), Pat Taylor (London).

Travel & Accommodation: The Whiteknights campus of the University of Reading is easily accessible by road or train and bus (or taxi). Reading also has excellent rail or coach links from Heathrow and Gatwick airports. Travel details and maps can be found at: http://www.reading.ac.uk/maps/whiteknights-struct.htm. En suite accommodation will be available in Whiteknights Hall on a first come basis, or delegates can make their own arrangements with local hotels (details available on request).

Communications: Part of the meeting will be devoted to oral presentation of selected abstracts and posters. There are two prizes of £250 each: the Clinical Science Young Investigator Award and the BSCR Young Investigator Award.

Registration (excluding accommodation): Free for BSCR members and £40 for academic non-members.

Bursaries: The Society will consider awarding travel grants of up to £200 to *bona fide* students.

The full programme, abstract pro-forma, meeting registration / accommodation forms and forms for application for student bursaries are available for downloading from the BSCR website (www.bscr.org).

Deadline for the submission of abstracts, registration and application for student bursaries: 2nd February, 2007.

Further enquiries: Enquires regarding the programme, registration or accommodation should be directed to Mrs Sue Aldridge, School of Pharmacy, FBS building, University of Reading, PO Box 226, Whiteknights, Reading RG6 6AP; Tel: +44 (0)118 378 4637; Fax +44 (0)118 378 6562 s.e.aldridge@rdg.ac.uk.

Enquires regarding BSCR membership or student bursaries should be directed to Prof. Barbara McDermott, BSCR Secretary, Therapeutics & Pharmacology, Queen's University Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL; Tel 02890-972242; Fax 02890-438346; b.mcdermott@qub.ac.uk