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Mark Boyett, Susan Coker, Cherry Wainwright

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Although the members of the Society continue to support the BSCR Bulletin by supplying articles on request we remain underwhelmed by the amount of unsolicited material we receive. Remember, if any society is to reflect the needs of its membership it is the responsibility of individual members to voice their opinions. The BSCR Bulletin is a forum for such communication. We would like to hear from you.

LETTER FROM THE SECRETARY

Dear Colleagues,

In the past two years, the Society has seen many changes. In particular, the Bulletin has become the major means of communication between members. This edition is no exception. For the first time, the Society is holding a postal ballot for the two new committee members. Please use your right to vote and return ballot papers to me by July 30th, marked BSCR Ballot. The research interests and experience of the three candidates are given on page 3 of the Bulletin. Furthermore, it is time to point out that three committee members will be resigning in December - namely, Alan Manning - the treasurer, Alan Williams and myself. In order for the Society to continue to improve communication we need to keep the committee filled with hard-working and motivated people. From my experience as Secretary, I know that the Society is full of such individuals. So, please, can you think hard and send nominations for candidates to me as soon as possible. The next two major meetings look exciting with details of the Autumn meeting inserted in this issue. There is an optional dinner on the evening of the Conference at a cost of £15 per head. Transport will be provided at the end of the meeting either to the restaurant or to the station. The dinner will finish in time for people to catch the last train to London. I look forward to seeing you there.

Anne-Marie L. Seymour
BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH ELECTION CANDIDATES


Susan Coker: Obtained her Ph.D. at Strathclyde University in 1980. Postdoctoral research fellow at Strathclyde 1980-1984. 1984-present, lecturer in Department of Pharmacology & Therapeutics, University of Liverpool. Research interests: acute myocardial ischaemia, arrhythmias, coronary flow, role of endogenous vasoactive substances such as 5HT, positive inotropic agents. Member of BSCR, ISHR and British Pharmacological Society. Organiser of forthcoming BSCR Spring meeting.


CELLULAR MECHANISMS IN CARDIAC HYPERTROPHY AND FAILURE

Autumn Meeting: Friday 24th November 1989
Venue: Academic Centre, John Radcliffe Hospital, Oxford

9.45 - 12.45 am  Biochemical Adaptations in Hypertrophy and Failure
                 (Chairman: Professor G. K. Radda)
B. Swynghedauw  Growth signals in cardiac overload
H. Taegtmeyer   Metabolic adaptation in hypertrophy and hypertension
A-M. Seymour    Models of hypertrophy and the role of phospholipids
P. Sugden       Protein synthesis in hypertrophy and failure

12.45 - 2.00 pm  Lunch in the Academic Centre

2.00 - 6.00 pm   Electrophysiological Changes in Hypertrophy and Failure
                 (Chairman: Dr G. Hart)
S. Houser        Membrane current changes in hypertrophy
G. Vassort      Calcium current, adrenoceptors and hypertrophy
C. Fry          Cardiac hypertrophy in the human heart
G. Cooper IV    The mechanical signal for cardiac hypertrophy induction
H. ter Keurs    Hypertrophy and the sarcoplasmic reticulum

6.00 - 6.30 pm  A.G.M.
7.30            Dinner at Studley Priory

There will be a one hour poster session during the afternoon and the number of posters presented will be limited by the available space. Abstract forms for posters are included in this edition of the Bulletin.
BSCR MEETING REPORT

On April 13th, members of the Society and invited speakers met in Glasgow, at the Kelvin Conference Centre, to participate in the Spring Meeting concerning the subject of Myocardial Repolarization and Refractoriness.

Dr George Hart (Oxford) opened the proceedings with a physiologically-oriented introduction to the meeting with a talk on mechanisms determining action potential duration. This was followed by an introductory talk on mechanisms of Class III antiarrhythmic activity, given by Dr E Carmeleit (Leuven, Belgium). The dependence of repolarization on whole organ dynamics was discussed by Dr Mark Boyett (Leeds), who focused on adaptation of action potential duration to heart rate. After the critical issues of (i) cellular and whole organ determinants of repolarization and refractoriness, and (ii) the nature of manipulation of the latter by drugs had been introduced, presentations focused on specific aspects of the subject. The general characteristics of drugs affecting repolarization and refractoriness were first considered. Dr Alan Higgins (Roche Pharmaceuticals, USA) spoke on the differences between Class I and Class III antiarrhythmics, and made some informed comments about how he sees the clinical applicability of such drugs being put to the test. Dr Helge Refsum (Tromso, Norway) focused on a different issue, the relation between positive inotropy and Class III activity.

After lunch the subject moved on to repolarization in the abnormal myocardium. Prof. Giel Janse (Amsterdam) began the session by considering the relation between repolarization and arrhythmogenesis in ischaemia. In his elegant presentation, Prof. Janse addressed some of the methodological problems associated with measurement of repolarization and refractoriness in ischaemia and during ventricular fibrillation (VF). In particular, it was pointed out that postrepolarization refractoriness during ischaemia can be misinterpreted, since the strong stimuli needed to excite ischaemic tissue can produce artifactual electrotonic excitation of nonischaemic tissue. Demonstration of local variation in refractoriness, and its dependence on local concentrations of extracellular potassium (K), in relation to its importance in initiation of VF was achieved by simultaneous mapping of voltage and K. The difficult problem of assessing refractory periods during VF was approached by assessing the steepness and amplitude of the voltage deflections. From the specific consideration of repolarization, Dr Martin Hicks and Prof. Stuart Cobbe (Glasgow) led us through a more general area by considering the electrophysiology of antiarrhythmic drugs in early ischaemia. This was followed by a presentation from Dr John Doherty and Prof. Cobbe (Glasgow) concerning repolarization changes in a model of congestive heart failure. The complex interrelationship between action potential duration and mechanical activity was addressed by Dr Max Lab and Dr John Dean (London) who focused our attention on the feedback occurring between myocyte tension and repolarization in the heart in situ. They attempted to answer the question whether physiologically relevant changes in load affect electrophysiology. As mechanical activity becomes disturbed in disease (e.g., wall tension changes in ischaemia) one can expect changes in refractoriness which might have potentially arrhythmogenic consequences. It was shown that rapid reductions in tension in papillary muscle prolongs Æquorin signal and prolongs action potential duration - but not by much. Whether this has any real significance to arrhythmogenesis remains to be determined.

In the final session our attention was turned to clinical matters. Dr Campbell Cowan (Leeds) gave a description of current understanding of repolarization in the human heart. It is known that the first areas to depolarize are the last areas to repolarize, with the epi- and endocardium showing similar patterns. This means that activation is inversely related to repolarization, serving to minimize dispersion of refractoriness, endowing the system with inherent stability. In heart failure this relationship is lost. It has been speculated that this dysfunction may tend to increase susceptibility to arrhythmias. Dr Ghazwan Butrous (London) took this subject a stage further by examining the issue of arrhythmias associated with repolarization abnormalities. Differences between early afterdepolarizations (promoted by sinus
tachycardia) and delayed afterdepolarizations (promoted by bradycardia) were considered, along with ramifications of the long QT syndrome (such as the relevance of T wave alternans to heterogeneity of repolarization). In the final presentation, Dr John Perrins (Leeds) discussed application of assessment of repolarization to the setting of pacemaker use. Modern pacemakers adjust their output in response to requirements, assessing QT interval by taking \(-\frac{dV}{dt}\) as the T position. The applicability of rate-responsive pacing was discussed.

In addition to the oral communications, a poster session took place during the intermissions. Selected abstracts from this session appear on this and the following page.

On behalf of all those who attended, I would like to thank Professor Cobbe and his colleagues for organizing an excellent and informative meeting.

Michael J. Curtis

BSCR MEETING ABSTRACTS:
Myocardial Repolarization and Refractoriness, Glasgow, Apr 13 1989

1

LACK OF CHRONIC ADAPTATIONAL CLASS III EFFECTS OF METOPROLOL ON VENTRICULAR REPOLARIZATION AND REFRACTORINESS IN AN ANIMAL MODEL
B. Stewart Manley and Stuart M. Cobbe.
Department of Medical Cardiology, Royal Infirmary, Glasgow, UK

The effects of chronic administration of metoprolol was studied in rabbits, using the endocardial paced-evoked response to measure local repolarization (stimulus-T interval) and refractoriness. Three groups of 7 rabbits were allocated to receive metoprolol 6mg/kg s.c. b.i.d., saline or no therapy. Recordings were made weekly for 4 weeks, shortly prior to the second daily injection. Stimulus-T interval was 113±7 ms (mean±SEM) before treatment and 113±6 ms after 4 weeks in the metoprolol group (NS), 107±3 and 109±9 ms respectively in the saline injected group, and 112±8 and 107±5 ms in the untreated group. In contrast to previous reports, we found no evidence of an adaptational increase in ventricular repolarization and refractoriness during chronic beta blockade.

TEDISAMIL (KC-8857): CLASS III ANTIARRHYTHMIC PROFILE IN RAT MYOCARDIUM
Michael J Curtis, Michael J Shattock. The Rayne Institute, St. Thomas' Hospital, London SE1 7EH, U.K.

The antiarrhythmic and electrophysiological profile of tedisamil (KC-8857), a putative class III agent, were examined in rat myocardium. Isolated rat hearts were perfused in the Langendorff mode with a solution containing (in mM) NaCl 118.5, NaHCO₃ 25.0, KCl 3, MgSO₄ 1.2, NaH₂PO₄ 1.2, CaCl₂ 1.4 and glucose 11.1, gassed with 95% O₂ and 5% CO₂, pH 7.4, 37°C. Hearts (n=12 per group) were subjected to a 10 min period of equilibration, 10 min of left coronary ligation and 10 min of reperfusion. Controls were compared with hearts perfused 5 min before ligation and throughout the experiment with 5 μM tedisamil. The % incidences of reperfusion-induced ventricular tachycardia (VT), ventricular fibrillation (VF), sustained VF lasting >120 sec (SVF), occluded zone size (OZ; % of ventricle weight), heart rate during the last minute of ischaemia (HR; beats/min) and coronary flow in the reperfused zone (CF; ml/min/g OZ) are shown.

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<th>VT</th>
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<tr>
<td>Controls</td>
<td>0</td>
<td>0</td>
<td>50</td>
<td>38.4±1.7</td>
<td>307±10</td>
<td>14.1±1.2</td>
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<td>5 μM Tedisamil</td>
<td>100</td>
<td>82</td>
<td>0*</td>
<td>35.8±1.7</td>
<td>169±8*</td>
<td>13.9±1.3</td>
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(*p<0.05)

Action potentials were recorded from rat papillary muscles superfused with medium similar to the above and paced at 0.5 Hz. Tedisamil 5 μM prolonged absolute refractory period (ARP) from 21 to 145 msec whilst causing only minor reductions in \(dV/dt_{max}\). In summary, tedisamil is a bradycardic class III antiarrhythmic which converts reperfusion-induced VF to sinus rhythm (causes defibrillation), but does not prevent VF initiation. Bradycardia equivalent to that seen with tedisamil is known to have no intrinsic defibrillatory activity. In conclusion, the antiarrhythmic activity of tedisamil appears to result from marked prolongation of ARP (a class III action).
3 EFFECTS OF ACUTE AND CHRONIC ADMINISTRATION OF AMIODARONE (AM) ON ELECTROPHYSIOLOGY AND ARHYTHMIAS INDUCED BY PROGRAMMED ELECTRICAL STIMULATION (PES) IN BEAGLES.


Recent studies on AM suggest that actions in addition to prolonged repolarisation may contribute to its antiarrhythmic effects. In the present study, acute i.v. administration of AM (2 + 10 mg/kg) to anaesthetised dogs with 5 day old myocardial infarcts (MI) failed to alter paced QT, whilst ventricular fibrillation (VF) inducible in 3 of 6 dogs was prevented, and the rate of ventricular tachycardia (VT) slowed from 456 to 407 beats/min (p=0.07). Atrial (ARP) and ventricular (VRP) refractory periods, AH and RR intervals were also prolonged (by 10, 5.3, and 25% respectively, p<0.01). Compared to untreated anaesthetised dogs surviving MI, ARP, VRP, AH and RR were increased in treated dogs (by 39, 14, 26 and 56% respectively, p<0.01), but paced QT was also prolonged (by 19%, p<0.01). The incidence of PES-induced VT was lower (p<0.05) in the AM group. 3/11 AM-treated dogs fibrillated compared with 6/9 controls. In conclusion, electrophysiological actions, e.g., bradycardia and slowed conduction, in addition to effects on repolarisation, may contribute to the antiarrhythmic efficacy of AM.

4 A DIPOLE MODEL DERIVED FROM REGIONAL DIFFERENCES IN MONOPHASIC ACTION POTENTIAL DURATION: ITS CORRELATION WITH THE ELECTROGRAM.


The problem of T wave changes characteristic of myocardial ischaemia in people with normal hearts is well known. Using a combination of adrenaline infusion, atrial pacing and beta blockade in man, we have previously shown these changes to be catecholamine and rate related. We have now used an animal model to investigate this further.

Monophasic action potentials (MAPs) were recorded simultaneously from three epicardial and one endocardial site in six landrace pigs. Restitution curves for MAP duration were obtained for steady states of 400 and 500ms and during adrenaline infusion and following beta blockade. Using the indifferent electrodes between any two MAP recording sites bipolar electrograms were obtained. In addition the MAP signals recorded from each corresponding pair were subtracted using a difference amplifier producing an ECG-like waveform. The changes in the T wave of this waveform were compared with the T wave changes in the corresponding electrogram in response to adrenaline, rate change and beta blockade.

The restitution curve for MAP duration was shifted down by adrenaline and upwards by beta blockade. Regional differences were observed and when these occurred the T wave changes derived from the algebraic subtraction of two MAP signals mimicked the T wave changes in the corresponding electrogram.

5 A MULTI-ELECTRODE CATHETER FOR SIMULTANEOUS PACING AND REGISTRATION OF ENDOCARDIAL MONOPHASIC ACTION POTENTIAL. SMC Hardman, T Biggs, WA Seed, MIM Noble, AJ Drake-Holland* SE Pugh. Department of Medicine and Academic Unit of Cardiovascular Medicine, Charing Cross and Westminster Medical School, St Dunstan's Rd, London W6 8RR and Department of Medicine, St George's Hospital, London SW17 ORE*

We have developed a multi-electrode catheter for electrophysiological studies which combines the standard pacing/electrogram facilities with monophasic action potential electrodes. The catheter comprises 2 standard electrodes for bipolar pacing or electrogram recording and 2 silver-silver chloride electrodes for monophasic action potential recording. Simultaneous pacing and monophasic action potential recording with this single catheter has been performed in 14 patients. We obtained undistorted action potential waveforms provided the pacing voltage was close to threshold (See Fig).

Fig. Patient record during pacing and simultaneous monophasic action potential recording using multi-electrode catheter.
LABORATORY PROFILE:
The Pharmacology Group
University of Bath

Research into cardiovascular pharmacology and pathophysiology has been carried out in Bath for many years. Our team has managed to pursue its research interests by attracting institutional and industrial support.

My first Ph.D. student was Derek Yellon (who spent several years studying diabetes, fatty acids and cyclic AMP before moving to the Rayne Institute, London). Since 1979, the group's interest has focussed on myocardial ischaemia. With my Ph.D. student of the time, Alan Daugherty (who subsequently moved to Peter Corr's Department in St. Louis), we undertook studies into the effects of alpha and beta adrenergic antagonism on arrhythmias induced by regional myocardial ischaemia. These studies were continued by Metin Avkiran (now working at the Rayne Institute and co-editing this Bulletin). Much to our surprise, it was found that although many sympatholytics inhibited arrhythmogenesis, the effects appeared to be unrelated to effects on the sympathetic nervous system or catecholamines (1).

These studies fostered our interest in the pathophysiology of myocardial ischaemia and reperfusion. Alan Daugherty went on to examine the role of potassium in arrhythmogenesis. At the same time a certain amount of interest was generated by the work of Mohamed Zakaria, which demonstrated a protective effect of free radical scavengers (glutathione, mannitol, catalase and superoxide dismutase) against reperfusion-induced arrhythmias. This study, published in 1983 (2) was the first to report such findings.

In recent years, and to the present day, the group has diversified its interests. Dr Anwar Baydoun and Dave Criddle are working on vascular reactivity and its modulation by pathophysiological products of ischaemia, and Pete Haddock is continuing the free radical work. The group also maintains an interest in potassium efflux during ischaemia, and in endothelin (3).

The research projects are currently funded by SERC and the pharmaceutical industry, with additional support from a joint project with Prof. David Hearse at the Rayne Institute, London, on free radicals and reperfusion, funded by the National Institutes of Health.

References:

Brian Woodward

ISHR UPDATE

The British Society for Cardiovascular Research shares many common interests (and much common membership) with the International Society for Heart Research (the ISHR). Indeed, joint membership of the two societies is available by writing to the BSCR Secretary (Dr A-M Seymour, Department of Biochemistry, University of Oxford, South Parks Road, OX1 3QU). For this reason, we thought you might be interested to know that the society has announced a few changes at the top, e.g., Nobuo Ito (Tokyo) replacing Winnifred Nayler (Melbourne) as president, Philip Poole-Wilson (London) replacing W. Kubler (Heidelberg) as treasurer and David Hearse (London) taking over from Naranjan Dhalla (Winnipeg) as Secretary General. These changes come into effect immediately.

SEMINARS:
Heart Research Lecture Series

July 27th 4.00 pm, Dr K. A. A. Fox: Positron emission tomography (PET) and myocardial reperfusion.

August 25th 3.00 pm, Dr S. S. Schreiber: The influence of work on genetic expression in the transplanted young heart.

Seminars are held at St. Thomas' Hospital, Lambeth wing, fourth floor. All are welcome.
MEETINGS CALENDAR


Sept 7-9, Rotterdam, The Netherlands: X European Meeting of the International Society for Heart Research (Post Graduate Medical Education, PO Box 1738, 3000 DR Rotterdam).

Sept 10-14, Nice, France: XI Congress of the European Society of Cardiology (ECCO, Rue Juste Olivier 22, 1260 Nyon, Switzerland).

Sept 13-15, Manchester, UK: British Pharmacological Society (J. MacLagan, Dept. Pharmacology, Royal Free Hospital School of Medicine, London NW3 2QG).

Oct 9-11, Munich, Germany: 3rd Annual Meeting, European Association for Cardio-Thoracic Surgery (EACTS, Interplan, Sophienstrasse, D-8000, Munich 2, FRG).


ADVERTISEMET

POST DOCTORAL OPPORTUNITY IN THE USA

The Cardiovascular Research Program at Hoffmann-La Roche in New Jersey consists of about 35 scientists engaged in multidisciplinary research into various aspects of acute myocardial ischemia and reperfusion, including disease-related changes in signal transduction and cell-cell interactions. The emphasis is on establishing a strong, innovative science base from which to develop novel therapeutic agents. The work presently involves studies in a wide range of systems, from cultured cells to sophisticated animal models of the human disease. There is a strong component of molecular biology, which we are applying at both the in vitro and in vivo levels. We are also engaged in some collaborative studies with several academic experts throughout the U.S.

I am presently looking for a post doctoral fellow to work with me on some of the more exploratory aspects of the program. If you feel you have some experience in some of the above mentioned areas and would like to spend up to three years in the U.S., working in an industrial environment, please contact me for further information.

Hoffmann-La Roche is situated in a pleasant urban area (New Jersey is not nearly so bad as most would have you believe!) about 12 miles West of New York City.

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