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THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH
Quarterly Bulletin

Edited by:

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LETTER FROM THE SECRETARY

Interesting Developments

The BSCR has grown over the last few years from a society narrowly concerned with cardiac muscle to one encompassing all aspects of the cardiovascular science. This change has reflected and at times, I hope, anticipated changes in the same direction by the ISHR, ESC etc. The result is a Society of over 500 members with now widely divergent interests. Hopefully, our strength will continue to grow from this breadth. It is equally true, however, that productive scientific interactions emerge from personal contacts and are best encouraged by small informal gatherings. There is therefore a current of feeling that BSCR meetings have become too formal and also that it is no longer possible stage a main meeting of interest to every member. Informal meetings should not be inconsistent with the Society's new standing, however, and are expressly catered for by workshops. Perhaps it is time to encourage the formation of "Interest Groups" within the Society and suggest that these groups organise (regular) informal workshops at which more of the membership can have the possibility of contributing. It is my view that the BSCR will have failed in its aim of promoting interchange of ideas unless such a development takes place. I am equally sure that British Cardiovascular Research will fail to keep up without the multi-group efforts that such contacts will foster.

Without wishing to discourage the spontaneity or increase the burden of organising a workshop, I should remind prospective organisers of the main conditions which the BSCR attaches to the use of its good name and its contribution of £400. Prior approval must be obtained from the Committee, where a guiding principle will be the benefit of the proposed workshop the membership as a whole. Meetings must be open to all members, normally without any registration fee. Accounts must be kept and any residue returned to the Society. Finally, I should stress that sufficient time must be allowed for advertising to the membership and registration.

Andrew Newby

CHAIRMAN'S COLUMN

Society Meetings

The Spring meeting in Cardiff was very well attended and provided excellent reviews of recent developments in the endothelial world. We are very grateful to our Secretary for his hard work in organising this meeting.

Future meetings are scheduled as follows:

Winter 1991: 5-6 December in London, "Regulation of coronary and systemic blood flow", organisers Dr. Nicholas Flores and Professor Desmond Sheridan, Academic Cardiology Unit, St. Mary's Hospital.

Spring 1992: Birmingham, "Myocardial receptors and innervation; therapeutic implications", organiser Dr. Peter Cummins, Department of Physiology, University of Birmingham.

Winter 1992: London, "Cardiac Myofilaments", organiser Dr. John Kentish, Department of Pharmacology, St. Thomas' Hospital.

Travel Bursaries for PhD Students

At the last Committee meeting a proposal was warmly accepted to provide up to 20 travel grants of £50.00 for PhD students to help with their expenses in attending the 1991 Winter meeting of the Society in London. This level of sponsorship perhaps does not match up with that of other, much more wealthy societies but, given what student grants are worth these days, I anticipate that it will be welcomed. The aim is to encourage young researchers to attend and
to contribute to our meetings (remember that if you submit a poster it will not be published, merely printed, if you so wish, in the Bulletin). The Society must remain, as it always has, an informal forum for exchange of results and ideas, and I hope that more contributions from young researchers will give us some freshness and vitality.

The bursaries can be applied for on forms which will be issued with the Bulletin and which must be countersigned by the research supervisor. Awards will be given on a first-come, first-served basis but if the scheme is over-subscribed, preference will be given to applicants whose research is directly related to the areas covered by the meeting. Applicants need not be submitting an abstract but they must be, or must become, members of the Society.

A BHF Award for the Bulletin

The Education Committee of the British Heart Foundation have renewed their support for the Bulletin with another year's grant of £750.00. We are most grateful for their continued interest in this worthwhile publication.

The Society Seeks Charitable Status

The Liverpool office of the Charity Commission is presently considering the case of our Society and we look forward to their reply. Technically we are at the "questionnaire" stage which means that the Commission has been furnished with detailed responses to a standard set of questions and with a sheaf of documents concerning the activities of the Society. One of these is a draft constitution which involves the Chairman applying a cold towel to his head and marrying our (exceedingly brief and informal) set of rules with a model constitution for a voluntary society provided by the National Council for Voluntary Organisations. My aim has been to make the constitution as flexible and as unrestrictive as possible, while complying with the requirements necessary for safeguarding the good running of a society and the interests of the Commission. In fact most of the requirements are sensible and represent good practice, and the Committee voted to submit the draft at its last meeting. In drawing up the draft I have been greatly helped by the legal department of the NCVO and by a local barrister. The Commission looks at the submission in detail at this stage, making enquiries with the Inland Revenue and ensuring that the constitution is sound. When it is satisfied we may expect to be invited to submit a formal application. Hopefully we shall be in a position, at the AGM next December, for members to vote on accepting the new constitution. Benefits which the Society may expect from charitable status include tax relief on profits from meetings and on interest from our accounts, rules to ensure good practice in running the Society, and the production of an annual report and an audited statement of accounts. And maybe the minutes will be signed from now on!

An Insurance Policy

I have been concerned that in these days of increasing litigation we should define and safeguard our position in the unlikely event of our being sued. At some but not all of our meetings local insurance cover is in place if, for example, a speaker falls off the podium, breaks his leg and wonders about taking legal action for failure to provide a handrail! The result is that the Committee have approved a liability insurance policy for the Society costing approximately £100 pa and covering us to a vast sum. But libel and slander are excluded, so do please be careful what you say! With that I hope these important housekeeping matters are at an end and next time I shall be able to write about cardiovascular research...

George Hart
BSCR MEETING ANNOUNCEMENT

Winter Meeting

REGULATION OF BLOOD FLOW

Thursday 5th - Friday 6th December 1991

Royal Pharmaceutical Society of Great Britain
London

Organisers: Dr Nicholas Flores and Professor Desmond Sheridan

SPEAKERS TO INCLUDE:

Dr W.M. Chilian, Texas, USA  
(British Cardiac Society Lecture)  
Segmental distribution and regulation of coronary microvascular resistance

Prof. C.C. Michel, London  
Regulation of flow and permeability in capillaries

Prof. G. Heusch, Essen, Germany  
Autonomic regulation of coronary arteriolar tone

Dr B. Lévy, Paris, France  
The structure and function of arteries in different experimental models of hypertension

Dr K. Parker, London  
Wave transmission in large arteries

ABSTRACTS: Members of the Society are invited to submit abstracts (on any topic) for oral or poster presentation.

REGISTRATION: Free to BSCR members and £25 to non-members. Registration forms and abstract instructions are included with this issue of the Bulletin. Further copies are available from:

Dr Nicholas A. Flores  
Academic Cardiology Unit  
St Mary's Hospital Medical School  
QEQM Wing  
South Wharf Road  
London W2 1NY

Tel: 071-725 6129  
Fax: 071-725 6732

IF YOU WISH TO ORGANISE A MEETING OR WORKSHOP, PLEASE CONTACT THE SECRETARY OF THE BSCR, DR ANDREW NEWBY (ADDRESS ON PAGE 2 OF BULLETIN).
2nd International Symposium

THE MAMMALIAN MYOCARDIUM
Biochemical and Physiological Mechanisms Underlying the Heartbeat

Sunday 26th - Wednesday 29th July 1992

The University of Leeds
Leeds, England

Organisers: Dr M. Boyett, Dr C. Orchard and Dr J. McCormack

This meeting is being organized in conjunction with the British Society for Cardiovascular Research and is being held under the auspices of the British Heart Foundation.

MAJOR TOPICS TO BE COVERED:
Ion channels, pumps and exchangers of the sarcolemma; ion flux and contractility; the sarcoplasmic reticulum; intracellular Ca²⁺ and excitation-contraction coupling; the myofilaments; cardiac metabolism and clinical aspects.

SPEAKERS AND CHAIRMEN TO INCLUDE:
B. Bean (USA), D. Bers (USA), E. Carafoli (Switzerland), R. Chapman (UK), M. Crompton (UK), D. Eisner (UK), P. England (UK), S. Fleischer (USA), H. Fozzard (USA), W. Giles (Canada), F. Hoffman (Germany), G. Isenberg (Germany), J. Kentish (UK), E. Lakatta (USA), W. Lederer (USA), G. Meissner (USA), D. Miller (UK), M. Morad (USA), D. Noble (Meeting Chairman, UK), M. Noble (UK), A. Noma (Japan), L. Opie (South Africa), H. Piper (Germany), J. Potter (USA), G. Radda (UK), B. Swynghedauw (France), H. ter Keurs (Canada), A. Williams (UK), D. Wray (UK).

ABSTRACTS: There will be poster sessions. Abstracts of all lecture and poster communications will be published in a special issue of the Journal of Molecular and Cellular Cardiology.


REGISTRATION: The conference fee will be around £200 and will include all accommodation, meals and coffee, conference materials and social events. The meeting is open to all interested and will be limited to about 250 participants. Further information can be obtained and preliminary registration can be indicated by writing to either Dr M. Boyett or Dr C. Orchard at:

Department of Physiology
University of Leeds
Leeds LS2 9JT

Tel: 0532-334265
Fax: 0532-334248
The symposium took place on 10-11 April 1991 at the University of Wales College of Medicine, Cardiff. The symposium attracted over 150 registrants, mainly from Britain, but with a contingent from Sweden and, of course, our guest speakers, Professor Russell Ross from the U. S. A. and Professor Arnold Herman from Belgium. The meeting was planned for 100, but last minute switching to a larger lecture theatre and flexibility on the part of the Residences Administration allowed us to seat and accommodate all those who applied to attend.

There were 14 poster submissions, which we managed to reduce to our limit of twelve by some amicable (I hope) arm-twisting. Posters were on display throughout the meeting (abstracts reproduced on pages 10-12). The almost overwhelming response to a symposium outside the traditional area of the old Cardiac Muscle Research Group was most gratifying.

Prof. Ross opened the meeting by giving the 5th Dame Honor B. Fell Memorial Lecture (organised jointly with the UWCM Tissue Culture and Cell Biology Club), and he acknowledged having spent formative years in Dame Honor's laboratory in Cambridge. Prof. Ross gave a pathologist's eye view of atherogenesis illustrated by quite splendid original micrographs. He laid stress on the sequence of events during atherogenesis in cholesterol fed monkeys, namely early ingress of monocytes and later generation of endothelial denudation and smooth muscle cell proliferation. He went on to describe important but differing roles for PDGF, TGFβ, IGF-1 and FGF in the generation of plaques, which had been elucidated from both tissue culture and whole animal models.

The remainder of the afternoon was devoted to discussion of endothelial interactions with other vascular cells. Dr. R. F. G. Booth reviewed the mechanisms underlying monocyte adhesion to endothelium and presented data on the role of the protein kinase C pathway obtained with novel selective inhibitors. Dr. J. D. Pearson described the role of endothelial calcium and protein kinase C in regulating the production of prostacyclin, nitric oxide and von Willebrand factor all of which modulate platelet-endothelium interactions. The role of nitric oxide production from endothelium and platelets themselves was taken up by Dr. M. Radomski. Endothelial control of vascular smooth muscle cell proliferation was reviewed by Dr. A. A. Soyombo, who presented data on potentially novel proliferation enhancing activity produced by the endothelial cells in organ cultures of human saphenous vein. Dr. P. L. Weissberg completed the afternoon's programme by describing the action of endothelins to potentiate PDGF-induced vascular smooth muscle cell proliferation.

Wednesday morning opened with four papers related to lipoprotein interactions with endothelium. Dr. P. D. Weinberg described the localisation of transendothelial lipoprotein transport using novel fluorescence microscopy methods and related this to sites prone to atheroma formation. Prof. A. G. Herman described the influence of models of hyperlipidaemia-induced atherogenesis on the function of endothelium as measured by impaired release of nitric oxide. Dr. D. S. Leake discussed the mechanisms by which endothelium and other vascular cell can modify low density lipoproteins to increase their atherogenicity. Dr. M. Jacobs then described the direct effects of normal and oxidatively modified LDLs to inhibit endothelial nitric oxide production.

The meeting was rounded off by a discussion of the importance of endothelium in clinically-encountered atherosclerosis from the cardiac surgeons point of view. In reviewing the literature and his own studies, Mr. G. D. Angelini achieved a perfect balance in conveying a serious message through the medium of a very light-hearted presentation.

Thanks are owing to Jill Allen, Gail Hughes and Wendy Simons, as well as many members of the Cardiff Cardiovascular Sciences Research Group, who bore the major burdens of organising the meeting. We are indebted to the British Heart Foundation for providing a visiting professorship to Prof. Ross and to the British Cardiac Society for a lectureship to Prof. Herman. The UWCM accommodated the meeting free of the usual charges. Finally, the meeting would have been impossible without the very generous financial support of Bayer (U. K.) Ltd.

Andrew Newby
READERS' VIEWS

“Power and impedance in the cardiovascular system”

While not producing any firm conclusions that could be applied to the assessment of mechanical performance in small mammalian hearts, the recent workshop at Lambeth Palace was important for highlighting the polarisation of engineering and physiology principles.

In engineering, the physical properties of complex electromechanical systems are described by terms that are amenable to accurate mathematical formulations. Terms like power transfer function and load impedance are carefully defined and related by correctly dimensioned equations.

By comparison, cardiovascular physiology is a pseudo-science based upon ill-defined parameters such as 'myocardial contractility' and 'inotropic effect', and functional assessment that frequently embodies assumptions and approximations that can only be justified by generalisations. Empirical parameters, such as dP/dtmax, rate-pressure product and tension-time integral are obtuse and nebulous. They are subject to complex problems of methodology and interpretation and have weak theoretical bases. The paramount difference between systems analysis in engineering and physiology is the greater mathematical rigour and precision of the engineering techniques. Physiology protects itself from the demand for mathematical determination by the excuse of the biological diversity and variation.

Potential applications for engineering techniques in physiology are numerous. For the analysis of cardiovascular function, electrical transmission line theory provides the relevant mathematical basis. The heart is then analogous to a transducer that converts chemical energy stored in molecules of ATP into mechanical energy. With negligible losses due to the formation of heat, this energy is used to perform work. A variable proportion of this work is internal. That is, it is used to overcome the source impedance of the heart - in more familiar terms, the sliding viscoelastic resistance. The ratio of internal to external work is a measure of myocardial efficiency.

External work results in the generation of blood flow and blood pressure in the proximal aorta and the rate of performing work is haemodynamic power. Power is a complex quantity in both conceptual and mathematical senses. The power spectrum consists of a frequency domain series of amplitude and phase relations. In this form, the external performance if the heart is comprehensively described, but the spectral data is difficult to interpret. A presentation that is easier to assimilate is to equate total haemodynamic power (\( \dot{W}_h \)) to the interdependent sums of mean (\( \dot{W}_m \)) and pulsatile (\( \dot{W}_p \)) power, potential (\( \dot{W}_p \)) and kinetic (\( \dot{W}_k \)) power, and cospectral (\( \dot{W}_s \)) (pressure and flow in-phase) and quadrature (\( \dot{W}_q \)) power (pressure and flow out-of-phase). All of these parameters are easily computed from the Fourier components of the pressure and flow signals. The subscript 's' = jw (j =√−1, w = 2πf, f = frequency) indicates that cospectral and quadrature power are dependent upon the heart rate. Haemodynamic power completely describes the external performance of the heart under any set of input and output loading conditions.

The load that the heart works against is the vascular impedance. For the left ventricle, it is the aortic input impedance. Like power, impedance is also complex and can be described by the impedance spectrum (\( Z_s \)), but the total impedance are the peripheral vascular resistance (Rp), characteristic resistance (Rc), arterial compliance (C) and inductance (L). By this process, parameters that are indeterminate by standard physiological techniques are revealed and the contributions of the arteries (Rc and C), arterioles (Rp) and blood volume (L) to the vascular load are distinguished.

Thus, cardiovascular function can be described by the computation of haemodynamic power and aortic input impedance. The technique is based upon elementary mechanics and electrical transmission line theory. It is equally applicable to isolated and in situ mammalian hearts, human patients and mechanical pumps. The measurement of blood pressure and flow can be made precisely and no assumptions concerning the relationships between cardiovascular function and the computed parameters are necessary. The specific relationships are:

\[
\begin{align*}
\text{Haemodynamic power} & : \dot{W}_h = C_s + D_s \\
\text{Aortic input impedance} & : Z_s = \frac{sL}{1 + sL/R_c} + \frac{\text{Rp}}{1 + sR_pC} \\
\dot{W}_m & = \dot{W}_p + D_p \\
\dot{W}_k & = \dot{W}_m + \dot{W}_k \\
Z_t & = f(\text{Rp}, \text{Rc}, \text{C}, \text{L})
\end{align*}
\]
Bibliography:

If you would like to set up a system for the computation of these parameters, the basic equations, recording and computation techniques can be found in the above references. If you have any problems, please contact me and I will do my best to help.

Gordon Wright
W. E. Dunn Unit of Cardiology, Dept of Biological Sciences, University of Keele, Staffs ST5 5BG
Tel: 0782-621111 Ext.3105

BOOK REVIEW
Principles and Practice of Cardiovascular Imaging
edited by
Gerald M. Pohost and Robert A. O'Rourke
Churchill Livingstone
942 pages, 959 illustrations
£115.00

It is extremely refreshing to open a major review text and to discover that the editors have adopted a rational approach to their subject that makes it accessible and relevant to readers from a diverse range of subspecialties. Drs. Pohost and O'Rourke are to be congratulated on the organisation of their book which is divided into three sections. The first subdivides cardiovascular imaging by modality with subsections on echocardiography, nuclear medicine, radiology and MRI. I was a little disappointed to discover that 'state of the art imaging' is given a disproportionate amount of space relative to its current clinical role (e.g. MRI covers 98 pages and angiography 40). Each subsection begins with a lucid and (mercifully) concise chapter on basic principles followed by chapters on the application of the modality to disease states. These chapters are (quite rightly) written by imaging experts rather than jobbing clinicians. Whilst this lends a quiet authority to the imaging aspects of the text, however, there are a number of controversial references to clinical practice, such as the assertion that cardiac catheterisation is essential for the differentiation of papillary muscle rupture and ventricular septal defect following myocardial infarction. Each subsection ends with a consideration of future trends. In such a rapidly moving field no text can hope to be comprehensive, but I was again disappointed at the omission of any reference to angioscopy and the relatively short section on trans-oesophageal echocardiography.

Clinical integration of the various modalities is much better covered in the second section where clinicians consider the rational use of imaging by disease process. This approach inevitably leads to some duplication and contradiction between the sections but these disadvantages are far outweighed by the benefits of clarity and ease of reference. These chapters are authoritative but not comprehensive. There is no chapter on the clinical use of imaging in aortic disease although this is adequately covered within the first section. The rational use of imaging is further considered in the third section which covers the important and often ignored issue of cost.

The text is copiously illustrated and eight pages are devoted to colour plates. Photographic reproductions are of such high quality that I would defy even a non-clinician to miss their diagnostic implications. Similarly, line drawings are clear and well annotated.

The broad scope of this book and its authoritative execution commends it as a reference text to all with an interest in cardiac imaging. The separation of clinical and technical aspects makes it accessible to the basic scientist as well as the clinician. It would make a welcome occupant of the library shelves of any cardiac department.

Clive Lawson
Transport of L-glutamine, a putative inhibitor of EDRF biosynthesis, was studied in cultured human venous endothelial cell monolayers. Uptake was mediated via a saturable carrier system dependent upon extracellular sodium and sensitive to inhibition by substrates for amino acid transport systems N (L-asparagine) and ASC (L-cysteine). By contrast, L-arginine (1 mM), β-2-amino-bicyclo-(2,2,1)heptane-2-carboxylic acid (1 mM) and 2-methylaminoisobutyric acid (1 mM), respectively, were ineffective inhibitors. In kinetic experiments calculated \( K_m \) and \( V_{max} \) values for L-glutamine transport were 0.14 mM and 2.5 pmol/min/μg protein, respectively.

**Expression of fibroblast growth factor mRNA and protein in the developing bovine heart.**

P. Cummins, S. Beestone, D. Chilton. Molecular Cardiology Unit, Department of Physiology, The Medical School, University of Birmingham, Birmingham, B15 2TJ, UK.

Basic (bFGF) and acidic (aFGF) fibroblast growth factors have been implicated in several growth processes in the heart, including myocyte proliferation and angiogenesis. The aim of this study was to establish the characteristics of the respective mRNA's, level of protein expression and cellular localisation of these factors. Total cell RNA was isolated from 20-30 week gestation bovine fetal ventricles and probed with cDNA's specific for aFGF and bFGF. Despite these mRNA's being present at low copy number and normally undetectable in the heart, bFGF mRNA was detected at 7.1Kb and aFGF at 3.8 Kb. These are compatible with mRNA sizes in other organs. ELISA of bFGF indicated levels of 380 to 520 μg/kg in the developing ventricle, considerably higher than previously determined. Immuno-cytochemical investigations using a polyclonal anti-recombinant bovine bFGF localised bFGF not only in blood vessels but also the cardiac myocytes. These results have important implications for the role of FGF's in myocyte proliferation.

**Balloon catheter de-endothelialisation of the nude rat carotid: response to injury in the absence of functional T lymphocytes.**

G.A.A. Ferns, M. Reidy, R. Ross. Dept of Pathology SM-30, University of Washington, Seattle WA 98195, USA.

We have studied the intimal proliferative response to balloon catheter de-endothelialization in congenitally athymic 'nude rats', that lack functional T cells. Significant intimal thickening was observed in both homozygous (nu/nu) and euthymic heterozygous (nu/+ ) animals by six days after injury, with further thickening occurring over the next four days. There were no significant differences in mean intimal: medial cross-sectional area, nor thymidine labeling of intimal and medial cells between the nu/nu and nu/+ animals at any time point. Approximately 1% of neo-intimal cells in both groups were leukocytes (OX-1 positive); 0.7% were macrophages (ED-1 positive). In neither group did T cells (OX-19 positive cells) constitute more than 0.1% of the neo-intimal population. These data suggest that T lymphocytes do not play a major role in the accumulation of neo-intimal cells. The presence of macrophages within the lesions raises the possibility that they may be involved in the recruitment and proliferation of smooth muscle cells. To aid in the interpretation of our in vivo data, we have also characterized the medial smooth muscle cells from nu/nu rat carotids with regard to their chemotactic and mitogenic responses to PDGF, TGF-beta and basic FGF.

**Coronary vascular endothelium releases factors which activate myocardial potassium channels.**

S Fort & M J Lewis, Department of Pharmacology & Therapeutics and Cardiology, University of Wales College of Medicine, Heath Park, Cardiff, CF4 4XN

We have investigated the role of the coronary vascular endothelium in the regulation of myocardial contractile performance by the intra-coronary infusion of substance P (SP) and bradykinin (BK) in isolated Langendorff-perfused ferret hearts. The results are expressed in mean ± s.e.m.

Following pentobarbitone anaesthesia the hearts were excised and perfused with Krebs Henseleit solution (1.25 mM Ca; 95% O2/5% CO2) at 37°C, containing 0.01 M acetylcholine and indomethacin. Left ventricular pressure was recorded via a fluid-filled latex balloon. SP and BK, both 10-6 M, continuously infused into the coronary circulation via an aortic root cannula produced a significant transient (<2 mins) reduction in peak pressure (16.2±6.3% and 27.0±4.2% respectively) and a fall in maximum rate of development of pressure (14.7±2.5 and 27.1±3.0% respectively). The SP- and BK-induced mechanical effects were not blocked by N-ω-nitro-L-arginine. The effects of BK were completely inhibited following removal of the endothelium by prior injection of a single bolus of Triton X-100. The BK-induced changes in mechanical performance were also inhibited by the prior infusion of glibenclamide, but not by tetrapentylammonium bromide (TPA). The SP-induced effects were blocked by TPA, but not by glibenclamide.

The present results indicate that the coronary vascular endothelium can modulate myocardial contractile performance through the release of one or more factors acting via myocardial K channels.
MODULATION OF ENDOTHELIAL ADHESION MOLECULE EXPRESSION BY PLATELET DERIVED IL-1

Interleukin 1 (IL-1) plays a critical role in the body's defense to infectious and inflammatory stimuli. Recent evidence has demonstrated the rapid cell associated expression of IL-1 by human platelets following activation (1). Since one of the earliest events in inflammation is the adhesion of platelets to injured endothelium, we have addressed whether platelet derived IL-1 is present in a functionally relevant form that can alter expression of the IL-1 inducible adhesion molecule intercellular adhesion molecule 1 (ICAM-1) on cultured endothelial cells.

Thrombin activated platelets enhanced expression of ICAM-1 antigen by both umbilical vein and saphenous vein endothelial cells. Unstimulated platelets induced much lower increases, whilst thrombin alone or supernatant from thrombin activated platelets stimulated a more prominent increase in ICAM-1 antigen expression. Pretreatment of thrombin activated platelets with antibodies specific for IL-1α and IL-1β, but not irrelevant antibodies, abrogated their capacity to enhance ICAM-1 expression. These results suggest that platelets may initiate and regulate some of the earliest events in the inflammatory response via the delivery of proinflammatory cytokines such as IL-1 to injured vascular endothelium.


INTIMAL PROLIFERATION IN AN ORGAN CULTURE OF HUMAN INTERNAL MAMMARY ARTERY
C.M. Holt, S.E. Francis, C. Clelland, G.D. Angelin, S. Rogers, P. Gadson. Department of Cardiac Surgery, University of Sheffield, Clinical Sciences Centre, Northern General Hospital, Sheffield.

Arterial intimal proliferation is an early feature of atherosclerosis. However its progression in humans is difficult to study. We therefore attempted to develop an organ culture model of intimal proliferation using segments of human internal mammary artery (IMA). Segments of IMA were dissected free from adventitia, carefully opened out and cultured, intimal surface uppermost for 14 days at 37°C in RPMI 1640 containing 30% foetal calf serum. In a separate experiment segments of IMA were de-endothelialized, prior to culturing. Tissue viability was assessed by ATP/ADP ratio, endothelial coverage by scanning electron microscopy and immunostaining for von Willebrand factor antigen and cell proliferation by autoradiography of histological sections. The ATP/ADP ratio of IMA did not significantly alter following 14 days in culture, 1.6±0.2 (Mean±SEM) vs 2.0±0.2 (n=10) indicating that tissue viability was maintained. Intimal proliferation was observed in histological sections of cultured IMA. Immunostaining revealed that these neointimal cells were weakly positive for α-actin, suggesting a differentiation towards a type of smooth muscle cell. Autoradiography showed proliferating cells in the neointimal layer with few dividing cells in the media. De-endothelialized IMA showed less neointimal thickening when compared with intact IMA, 21±2 μm vs 36±7 μm (n=6, p<0.05) as well as a reduced number of dividing cells per mm intimal length, 4.1±0.6/mm vs 6.7±1.3/mm (n=6). Thus, an organ culture model of human arterial intimal proliferation has been established. De-endothelialization results in diminished neointimal thickening, providing evidence for an endothelial derived proliferation enhancing factor. Inhibitors of this factor may therefore present new possibilities for therapy.

DISTRIBUTION OF MATURE IMMUNOREACTIVE ENDOTHELINS AND THEIR PRECURSORS IN HUMAN VASCULAR TISSUE. P.G. Howard, C. Plumpton, and A.P. Davenport. Clinical Pharmacology Unit, University of Cambridge, Cambridge U.K. CB2 2QO.

We have raised five polyclonal antibodies in rabbits to compare the distribution of mature ETs, big ET-1, big ET-2, and big ET-3 immunoreactivity in human vascular tissue. Vessels tested include: saphenous vein (n=7), mesenteric vein (n=3), mesenteric artery (n=4), and internal mammary artery (n=4). ELISA showed that the C-terminal heptapeptide of ET-1 cross-reacts with ET-1, ET-2, and ET-3 but not with the Big ETs. Antisera directed to C-terminus of Big ETs (proendothelins) only recognised the corresponding Big ET peptide. Mature ET antisera and Big ET-1 antisera stained the cytoplasm of endothelial cells and the vasa vasorum in all vessels while immunoreactive Big ET-3 could not be detected at concentrations as high as 1:100. However, Big ET-2 immunoreactivity showed a more intense staining as compared to controls using pre-immune sera or normal rabbit sera. These results provide evidence for a source of ET-like peptides in vascular tissue. (We thank the BHF for continued support).

EFFECT OF PENTOSAN POLYSULPHATE, HEPARIN AND A HEPARIN CORTICOSTEROID COMBINATION ON INTRACELLULAR LEVELS OF tPA AND PAI-1 IN HUMAN ENDOTHELIAL CELLS. N.B. Martin, A. Jamieson, and D.P. Tuffin. ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG.

In addition to their well recognised anti-coagulant effects, heparin-like compounds are also reported to induce pro-fibrinolytic activity. This response may contribute to the anti-angiogenic actions reported for these compounds, and is particularly evident with heparin corticosteroid combinations. The aim of this study was to further investigate the pro-fibrinolytic action of these compounds by measuring intracellular levels of tPA and PAI-1 in cultured human umbilical vein endothelial cells. Pentosan polysulphate (100 μg/ml), heparin (90 μg/ml) and a heparin (90 μg/ml) + hydrocortisone (100 μg/ml) combination (but not hydrocortisone alone) significantly increased intracellular tPA antigen. This effect of monotherapy was more dramatic with the heparin steroid combination. A parallel reduction in intracellular levels of PAI-1 was also observed. If mirrored in vivo, this response would lead to increased plasma fibrinolytic capacity which in turn could contribute to the anti-angiogenic action of these compounds.
THE USE OF L-ARGININE HYDROCHLORIDE AS AN ACUTE HYPOTENSIVE AGENT DURING ANAESTHESIA.

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We are evaluating the use of L-arginine as an hypotensive agent in anaesthetic practice and whether its reported hypotensive action can be exploited clinically.

A positive inotrope and a vasodilator, L-arginine has been used in the anaesthetic management of patients who have undergone major surgery. We report here the results of a double-blind, placebo-controlled study of L-arginine in patients undergoing major surgery.

We studied 20 patients, 10 in each group, who received either L-arginine or placebo. Both groups had similar baseline characteristics. The L-arginine group received L-arginine (10 mg/kg) in 500 ml of saline over 30 minutes. The placebo group received the same volume of saline over the same period.

We measured mean arterial pressure (MAP), mean arterial wedge pressure (PAWP), central venous pressure (CVP), heart rate (HR), and cardiac output (CO) before, during, and after the infusion. We also measured plasma L-arginine levels before and after the infusion.

MAP, PAWP, and CVP all fell within 5 min of giving L-arginine and recovered 10 min after stopping the infusion. No significant changes occurred in arterial oxygen tension or blood glucose levels.

L-arginine appears to reduce systemic blood pressure in a gentle and controllable fashion and is an attractive alternative to other agents as it may be increasing endogenous levels of EDRF thereby controlling vascular tone in perhaps a more physiological fashion.


THE EFFECT OF APROTININ ON PLATELET-ENDOTHELIAL CELL REACTIONS

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We have shown previously that the serine protease inhibitor Aprotinin will dramatically reduce blood loss after open heart surgery and is associated with a reduction in template bleeding time. The present study investigated the effects of Aprotinin (30 μM) on normal and stimulated human umbilical vein endothelial cells (HUVEC) with respect to (1) the adherence of platelets and (2) release of pro- and anti-aggregatory substances. The mean basal adherence of platelets to unstimulated HUVEC was 3.3 ± 0.4 (n=12) which increased to 8.5 ± 2.1 (n=12) following pretreatment with HUVEC with 10 μM thrombin (p<0.001). Aprotinin caused significant decreases in basal adherence of platelets to HUVEC to 2.5 ± 0.4 (n=12) and stimulated adherence to 6.3 ± 2.1 (n=12) p<0.009.

l-methyl arginine enhanced stimulated adherence to 12.5 ± 2.5 (n=4) and this was not altered significantly by Aprotinin. The effect of Aprotinin on release of prostacyclin (PGI2) and von Willebrand factor (vWF) from HUVEC was also investigated. PGI2 release was increased following stimulation with thrombin, histamine, and poly-L-lysine (6.10 and 2 fold respectively), vWF release was increased following stimulation with thrombin, histamine, poly-L-lysine and phospholipid myristate acetate (3,2 and 4 fold). Aprotinin had no significant effects on these release reactions.

CHARACTERIZATION OF NITRIC OXIDE SYNTHASE IN CULTURED ENDOCARDIAL CELLS

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The endocardial cells lining the interior chambers of the heart have recently been shown to release a humoral agent with properties indistinguishable to those of endothelium-derived relaxing factor (EDRF). Since nitric oxide (NO) accounts for the biological activity of EDRF, we have now examined porcine endocardial cells for the presence of NO synthase, the enzyme which synthesizes NO from L-arginine (L-arg). In bioassay experiments, perfused from a column of endocardial cells grown on microcarrier beads caused relaxation of a segment of endothelium-denuded pig coronary artery. This effect was potentiated in the presence of superoxide dismutase and catalase and abolished by hemoglobin (0.5 μM) or N^'-monomethyl-L-arginine (L-NMMA) (50 μM). Cytosol was prepared from endocardial cells by sonication and ultracentrifugation and the rate of NO synthesis was measured spectrophotometrically. Addition of L-arginine (0.3-30 μM) in the presence of NADPH (100 μM) and CaCl2 (200 μM) caused a concentration-dependent increase in the rate of NO formation to a maximum of 5.67 ± 0.80 pmol/min/mg protein in the absence of added L-arg, or if D-arg (30 μM) was substituted for L-arg, or if NADPH was omitted from the reaction mixture, the rate of NO synthesis was below the limit of detection (<0.1 pmol/min/mg protein). If NADPH was added but NADH (30 μM), abolished NO formation, which was partially reversed by addition of L-arginine (300 μM) (41.7 ± 4.1%, n=3).

Release of NO was not detectable in the presence of EGTA (1 mM). Readability of calcium stimulate NO synthesis in a concentration-dependent manner (EC50 0.65 ± 0.10 μM, n=3). Thus we have shown for the first time that endocardial cells have a constitutive NO synthase which is L-arg, calcium and NADPH dependent, similar to that found in vascular endothelial cells. The physiological role of endothelium-derived NO remains to be investigated.

Autoradiographic localization and characterisation of calcitonin gene-related peptide (CGRP) receptor in porcine coronary artery (CA) in a higher density in small coronary artery (SCA). The receptor binding density in small coronary artery (SCA) and large coronary artery (LCA) was 114 fmol/mg protein, whereas in the SCA this was 25 fmol/mg protein. Our results have demonstrated a higher density of specific binding sites for CGRP in small porcine CA, which is consistent with previous pharmacological studies. CGRP might play a more important role in the regulation of blood supply to the myocytes through its receptor in the small CA.