Advanced Medicine 17

Edited by D P Jewell

Royal College of Physicians of London

ADVANCED MEDICINE 17

Edited by
D P Jewell

Royal College of Physicians of London

PITMAN MEDICAL

First Published 1981

Catalogue Number 21.3279.81

Pitman Books Limited
39 Parker Street, London, WC2B 5PB

Associated Companies:
Pitman Publishing Pty Ltd, Melbourne
Pitman Publishing New Zealand Ltd, Wellington

British Library Cataloguing in Publication Data

Advanced medicine. – 17
1. Medicine – Periodicals
610'.05 R111

ISBN 0-272-79633-6
ISSN 0308-3888

Printed and bound in Great Britain
at The Pitman Press, Bath

ADVANCED MEDICINE 17

FOREWORD

The seventeenth Advanced Medicine Conference was held at the Royal College of Physicians in February 1981. The programme, as in previous Conferences, consisted of reviews drawn from widely different aspects of medicine. The aim was to present a clinical update alongside the scientific work which has been the basis for advances in diagnosis, management and our understanding of pathogenesis. Two sessions were allocated to topics of general interest having enormous clinical potential, namely, prostaglandins and endorphins, which led into areas as diverse as obstetrics, acupuncture and psychiatry.

This volume represents the proceedings of the Conference and I am grateful to the contributors whose high standard of presentation ensured a successful and stimulating meeting. I would like to thank all the College staff who organise these Conferences so efficiently. Finally, my thanks go to Mrs Betty Dickens and her staff at Pitman Books Ltd whose indefatigable energy allow this book to be published so rapidly.

D P Jewell

LIST OF CONTRIBUTORS

A B Atkinson MD, MRCP	Senior Medical Registrar, MRC Blood Pressure Unit, Western Infirmary, Glasgow
M Bamber MRCP	Research Fellow, Royal Free Hospital, London
J R Batchelor MA, MD, FIBiol	Professor of Tissue Immunology, Hammersmith Hospital, London
S P Borriello BSc	Visiting Worker, Clinical Research Centre, Medical Research Council, Northwick Park Hospital, Harrow
J J Brown FRCP, FRS(Ed)	Consultant Physician, MRC Blood Pressure Unit, Western Infirmary, Glasgow
A M M Cumming RGN	Clinical Nursing Officer, MRC Blood Pressure Unit, Western Infirmary, Glasgow
M Davis MD, MRCP	Consultant Physician, The Liver Unit, King's College Hospital, London
M de Swiet MD, MRCP	Consultant Physician and Senior Lecturer, Queen Charlotte's and Brompton Hospitals, London
J Fidler MB, MRCP, MRCOG	Senior Registrar, Queen Charlotte's Hospital, London
T H Flewett MD, FRCP, FRCPath	Director, Regional Virus Laboratory, East Birmingham Hospital, Birmingham
D G Grahame-Smith PhD, FRCP	Rhodes Professor of Clinical Pharmacology, Honorary Director, MRC Unit of Clinical Pharmacology, Radcliffe Infirmary, Oxford
C J Hawkey BA, MRCP	Research Fellow, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford
H J F Hodgson DM, MRCP	Senior Lecturer in Medicine, Royal Postgraduate Medical School, London
J I E Hoffman MD, FRCP	Professor of Pediatrics, University of California, San Francisco, California, USA

P Howard DM(Oxon), FRCP	Reader in Medicine, Royal Hallamshire Hospital, Sheffield
R Howell BSc, MB MS	Senior House Officer, Queen Charlotte's Hospital, London
C Isles MD, MRCP	Medical Registrar, Royal Infirmary, Glasgow
G Janossy MD, PhD	Reader in Immunology, Royal Free Hospital, London
W J Jeffcoate MB, BChir, MRCP	Consultant Physician and Endocrinologist, City Hospital, Nottingham
H E M Kay MD, FRCP, FRCPath	Consultant Clinical Haematologist, Royal Marsden Hospital, London
H E Larson MD, MRCP	Member of the Scientific Staff, Clinical Research Centre, Medical Research Council and Honorary Consultant Physician, Northwick Park Hospital, Harrow
J M Ledingham MD, FRCP	Professor of Medicine, The Medical Unit, The London Hospital, London
G de J Lee MD, FRCP, MB BS	Consultant Physician and Cardiologist, John Radcliffe Hospital, Oxford
E Letsky MB BS, MRCPath	Consultant Haematologist, Queen Charlotte's Hospital and Hospital for Sick Children, Great Ormond Street, London
A F Lever FRCP, FRS(Ed)	Consultant Physician, MRC Blood Pressure Unit, Western Infirmary, Glasgow
S L Lightman MA, MB, BChir, MRCP(UK)	Wellcome Senior Lecturer, St Mary's Hospital Hospital Medical School, London
S Lipton FFARCS	Director, Centre for Pain Relief, Walton Hospital, Liverpool
W A Littler MD, FRCP	British Heart Foundation Professor of Cardiovascular Medicine, University of Birmingham, Honorary Consultant Cardiologist, East Birmingham and Queen Elizabeth Hospitals, Birmingham
A Mackay MD, MRCP	Medical Registrar, Department of Cardiology, Royal Infirmary, Edinburgh

A V P Mackay MA, BSc(Pharm), PhD, MRCPsych	Physician Superintendent, Argyll and Bute Hospital, Argyllshire and MacIntosh Lecturer in Psychological Medicine, University of Glasgow
G P McNicol MD, PhD, FRCP, FRCPath, Hon FACP	Professor of Medicine, The General Infirmary, Leeds
R Mansilla Tinoco MB	Department of Clinical Pharmacology, Royal Postgraduate Medical School, Hammersmith Hospital, London
J R A Mitchell BSc, MD, MA, DPhil, FRCP	Professor of Medicine, University Hospital, Queen's Medical Centre, Nottingham
M D Mitchell MA, DPhil, MRC	Senior Fellow, John Radcliffe Hospital, Oxford
S Moncada MD, PhD	Head of Department, Prostaglandin Research, Wellcome Research Laboratories, Beckenham, Kent
A J Newman-Taylor MRCP(UK)	Brompton Hospital, London
H G Prentice MB, BS, MRCP, MRCPath	Senior Lecturer and Honorary Consultant, Royal Free Hospital Medical School, London
A Richens BSc, PhD, FRCP	Professor, Department of Pharmacology and Materia Medica, Welsh National School of Medicine, Cardiff
J I S Robertson FRCP, FRS(Ed)	Consultant Physician, MRC Blood Pressure Unit, Western Infirmary, Glasgow
D B Silk MD, MRCP	Consultant Physician, Central Middlesex Hospital, London
M P E Slack MA, MB, MRCPath	University Lecturer in Bacteriology, John Radcliffe Hospital, Oxford
H C Thomas BSc, PhD, MRCP	Senior Wellcome Fellow and Consultant Physician, Royal Free Hospital, London
A C Turnbull MD, FRCOG	Professor of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford
C W G Turton MD, MRCP(UK)	Senior Medical Registrar, Brompton Hospital, London

J R Vane FRS	Director of Research, Wellcome Research Laboratories, Beckenham, Kent
P G Wheeler DM, MRCP	Consultant Physician, The William Harvey Hospital, Ashford, Kent
C P Willoughby MA, DM, MRCP	Research Fellow in Gastroenterology, John Radcliffe Hospital, Oxford

CONTENTS

The Lilly Lecture

THE PATHOPHYSIOLOGY OF SUBENDOCARDIAL ISCHAEMIA: OLD CONCEPTS AND NEW DIRECTIONS

J I E Hoffman

Electrocardiographic changes of subendocardial ischaemia or histological subendocardial necrosis or fibrosis occur in a wide variety of cardiac diseases, with or without normal coronary arteries. These changes are noted in aortic stenosis or incompetence, cyanotic congenital heart disease, pulmonary hypertension, anaemia, shock and hypothermia. Haemorrhagic subendocardial necrosis is common in patients who die after open heart surgery [1–3].

The subendocardial changes are generally attributed to ischaemia. Ischaemia indicates an imbalance between blood supply and tissue oxygen demands, so that insufficient oxygen is delivered and insufficient metabolites (mainly carbon dioxide and hydrogen ion) are removed. The imbalance that causes ischaemia can be due to normal muscle demands but decreased blood flow as in coronary arterial disease, or can occur if blood flow does not rise enough to match increased tissue demands, as in aortic stenosis.

Ischaemia might occur preferentially in subendocardial than more superficial muscle either because of a higher subendocardial oxygen demand or a tendency to selective subendocardial underperfusion. Some studies report about a 20 per cent greater oxygen usage of subendocardial muscle, but this difference in oxygen demand is probably only a minor factor since almost all studies of subendocardial ischaemia have demonstrated an absolute or relative decrease of subendocardial blood flow [2]. This is particularly important because at rest the left ventricle has a very high oxygen consumption per unit mass and oxygen extraction from coronary blood flow is nearly maximal. Increased oxygen demands, as with exercise, are met almost entirely by increasing coronary flow, and there is little margin for further oxygen extraction [3]. Therefore, any decrease in subendocardial blood flow relative to needs soon leads to subendocardial anaerobic metabolism, decreased contractile performance and, if long continued, cell death [4–6].

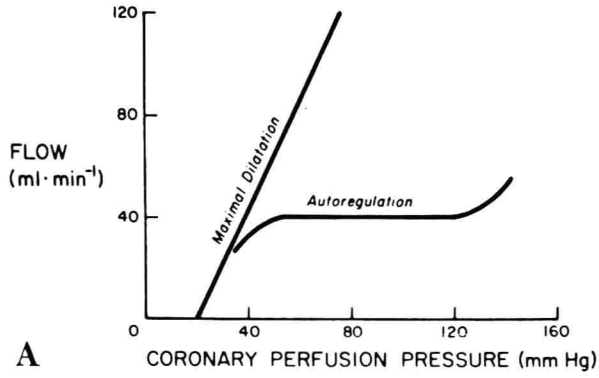
Autoregulation of coronary blood flow

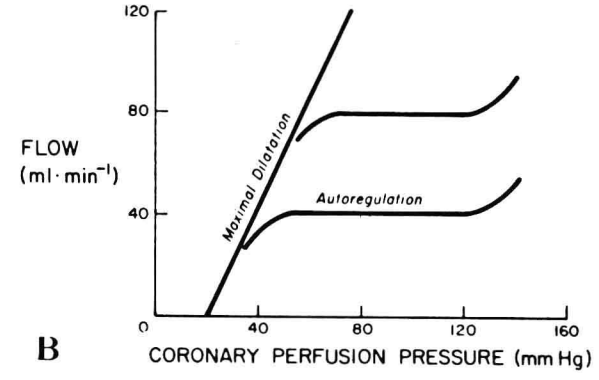
Normally, coronary blood flow is autoregulated: if tissue need increases or perfusion pressure decreases, then vessels dilate in all layers of the left ventricle and regional flows remain matched to demand. With each added increase in tissue need or decrease in perfusion pressure further vasodilatation takes place until eventually a limit to compensatory vasodilatation is reached. This limit is not reached at the same time in all layers; recent studies have shown that maximal vasodilatation is reached earliest in subendocardial muscle [7,8]. When this limit is reached, then flow becomes pressure dependent; that is, since vessels are maximally dilated, flow is directly proportional to pressure. Thus, if perfusing pressure decreases, subendocardial flow will decrease and ischaemia will occur. Alternatively, if pressure remains constant but tissue demands increase, subendocardial flow will not be able to increase and once again ischaemia will occur. Subepicardial flow per gram, however, remains appropriate for tissue needs and exceeds subendocardial flow per gram.

Some characteristics of coronary blood flow are displayed diagramatically in Figure 1A, in which coronary perfusing pressure is plotted against total left ventricular coronary blood flow during autoregulation and again during maximal coronary vasodilatation in the same heart. During autoregulation, flow remains constant (horizontal line) as perfusing pressure decreases, until eventually total flow decreases because subendocardial flow begins to decrease. The oblique line indicates the flows attainable at any perfusing pressure when all vessels are widely dilated. The distance between the autoregulated and maximally dilated lines is the *coronary vascular reserve*, and indicates the extra flow that can be achieved at any pressure once the vessels are maximally dilated. As perfusing pressures decrease, vascular reserve decreases even if resting (autoregulated) flow is kept constant.

Figure 1B shows what happens when the resting level of flow is increased, as happens with exercise, anaemia or ventricular hypertrophy. Autoregulated flow is higher (upper horizontal line), but still operates as perfusion pressure is lowered until once again total flow is reduced when subendocardial flow can no longer be autoregulated. However, the pressure at which autoregulation fails is higher than it had been with lower resting flows because coronary vascular reserve is lower at all perfusing pressures at these higher flows. In fact, the slope of the line of maximal vasodilatation shows that autoregulation must fail at a higher pressure when the level of autoregulated flow is higher.

A third important variable is shown in Figure 1C. The solid lines represent normal values as shown in panel A, and the dashed lines indicate what might happen in cyanotic heart disease. The oblique line of maximal vasodilatation has a lesser slope because of the increased viscosity of polycythaemic blood [9,10]. The autoregulated line indicates a flow that is not lower than normal because of hypoxaemia. As compared to normal, there is a lower coronary vascular reserve





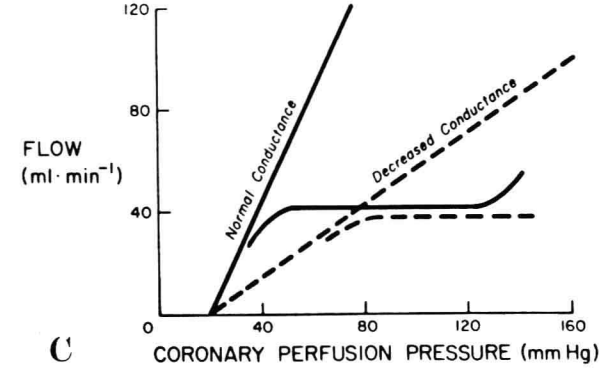


Figure 1. Autoregulation of coronary blood flow. See text for details

in polycythaemia, and autoregulation fails at a higher pressure.

In all these pathophysiological abnormalities, coronary vascular reserve is reduced at all perfusion pressures, and the pressure at which autoregulatory compensation fails is greater than normal. Furthermore, as mentioned above, when autoregulation fails and total coronary flow decreases, the reduced flow is initially subendocardial; flow to more superficial muscle layers tends to remain constant.

Subendocardial flow and vascular reserve

Three major mechanisms can be invoked to explain why coronary vascular reserve is exhausted earlier in subendocardial than more superficial muscle. Firstly, the duration of perfusion may be shorter in subendocardial muscle, since in systole myocardial compressive forces may squeeze deep vessels closed, but permit flow to continue in superficial muscle; as a result subendocardial muscle would be perfused only in diastole but more superficial muscle would be perfused throughout the cycle. Secondly, there may be fewer or smaller vessels in the subendocardial muscle, thereby decreasing the maximal achievable flow in that layer. Thirdly, since most left ventricular flow is diastolic, there might be greater opposition to diastolic flow in deep than in superficial muscle.

Duration of perfusion

About 75 to 80 per cent of left coronary arterial flow takes place in diastole, and this has been attributed to systolic myocardial compression of intramural coronary vessels. That compression might be uneven across the left ventricular wall was first noted by Johnson and di Palma in 1949 [11]. They measured regional myocardial pressures by placing fluid droplets or tubes in the muscle, and concluded that in systole intramyocardial pressures were highest in the subendocardial muscle, where they equalled or exceeded pressure in the ventricular cavity, and decreased to low values in the subepicardial muscle. Since then, many investigators with different methods have reached similar conclusions, agreeing with the general patterns but differing as to absolute pressures [2,12]. The likely reason for the differences was described by Gregg and Eckstein [13] who showed that the pressure measured in the myocardium depended on the degree of local distortion produced by the droplet, tube or needle inserted; these criticisms apply equally well to modern studies with small solid state pressure transducers.

Engineering models of radial stresses across a thick-walled structure like the left ventricle also infer a stress equal to the cavity pressure just beneath the endocardium and decreasing to zero at the epicardial surface. However, the detailed results of such models vary with the initial assumptions made; for example, different stress distributions are obtained by considering inhomogeneity, anisotropy, large strains, irregular cavity shape, and torque [14,15]. We have no way of knowing if all the relevant assumptions have been considered. Two other findings also

make the engineering approach of uncertain value. By definition, radial stresses are zero across the wall of a beating empty heart with zero cavity pressure; nevertheless, Baird, Goldbach and de la Rocha [16] found in such a heart that intramyocardial pressures in systole were similar to those in the normal beating heart. Secondly, Caulfield and Borg [17] studied the collagen framework of the heart by scanning electron microscopy, and noted changes in systole consistent with tension on collagen fibres pulling vessels open. No existing direct methods or models can indicate what happens on this microscopic scale.

In addition to uncertainty about intramyocardial pressures in systole, we are no longer sure that much left ventricular muscle is perfused in systole. Although a flowmeter at the origin of the left coronary artery shows about 20 to 25 per cent of the flow to be systolic, it is likely that at rest most of this blood distends extramural coronary arteries which have a systolic volume change of about this amount [18]. Furthermore, Tillmanns and his colleagues [19] reported that by direct examination under the microscope there was no forward flow in systole in arterioles more than about 0.5mm below the epicardium. It is true that with maximal flows there might be systolic perfusion of more of the superficial muscle. However, in the commonest cause of subendocardial ischaemia, that seen with coronary arterial disease, total coronary flow is decreased and it is unlikely that differential perfusion times explain the subendocardial underperfusion.

Vascular conductance

The second mechanism, a lower maximal vascular conductance in the subendocardial muscle, is no longer tenable. Several recent studies have shown that in the arrested relaxed heart, maximal conductance is about 60 per cent greater in subendocardial than subepicardial muscle [7,20]. This greater subendocardial vascular conductance cannot possibly be the cause of subendocardial ischaemia.

Opposition to diastolic flow

This leaves the third mechanism to consider, namely a greater opposition to diastolic flow in deep than superficial muscle. Consider first what happens to total left coronary arterial flow, as first reported by Bellamy in 1978 [21]. In a long diastole, coronary flow and pressure decline more or less exponentially, and flow measured by a flowmeter on the left circumflex coronary artery reaches zero when coronary arterial pressure is about 45mmHg. If these diastolic pressures and flows are measured every 0.1 seconds, then the pressure-flow plot is linear with an intercept on the pressure axis at zero flow (Pfo) of 45mmHg. (This does not negate the concept of autoregulation which refers to average measurements over the cardiac cycle.) When coronary vessels are maximally dilated, Pfo is about 20mmHg.

These pressure-flow plots are reasonably linear, although careful recent studies