Science, medicine, and the future

The future of the management of ischaemic heart disease

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Abstract

Ischaemic heart disease will kill over 150 000 people in the next year in Britain, more than any other single disease process, and cost more than £1.4bn in health care alone. Faced with the continuing problems arising from ischaemic heart disease cardiologists are moving from technology based solutions to basic sciences. This article explains how basic science may contribute to new understanding and treatments for patients with ischaemic heart disease. Highlighted are three problems which face any clinical cardiologist on a daily basis and for which basic science may provide solutions: the uncertainty of plaque stability in coronary disease; restenosis after percutaneous transluminal angioplasty; and the shortage of organs for cardiac transplant programmes for patients with heart failure.

Introduction

"Well, tell me, how does your research help my patients in the clinic?" This is a question many cardiologists who have undertaken research during their training will remember hearing with a sinking feeling as they dealt with an interview committee. However, the application of basic science research in cardiology now offers the real prospect of neutralising this intentionally hostile interrogative mantra.

For the past 40 years almost all problems within the heart have been perceived either mechanically or structurally. The unravelling of the whole of valvular and congenital heart disease with the diagnostic developments of cardiac catheterisation and echocardiography and the stunning therapeutic successes of cardiac surgery reinforced the cardiologists' focus on the "mechanical fix." Ischaemic heart disease yielded less easily to this way of thinking but the technologically driven, mechanically minded cardiologist turned into the interventionalist, and some problems of ischaemic heart disease are yielding under the onslaught. Undoubtedly their patients are helped—but only in part and, often, only temporarily. Winning wars after battles are lost needs a change of tactics, and the change in cardiology is the embracing of basic sciences.

In this article I will show how basic science might influence the management of patients with ischaemic heart disease and examine the real clinical problems of the variability of disease, restenosis after percutaneous transluminal angioplasty, and the shortage of donor

Possible future developments

- Understanding of the determinants of the mode of presentation of ischaemic heart disease
- Identification of new targets for the pacification of atherosclerotic plaques
- Treatments to limit the vessel response to injury after angioplasty and thus prevent clinical restenosis
- Ready availability of donor organs for cardiac transplantation

hearts for transplantation programmes. Such advances will be important since ischaemic heart disease will kill over 150 000 people in the next year in Britain, more than any other single disease process, and cost more than £1.4bn in health care alone.¹

Why do cases of ischaemic heart disease present and progress differently?

Coronary angiograms give detail about luminal narrowings in epicardial coronary arteries and, aided by far from precise tests of inducible ischaemia, cardiologists guess which lesions limit coronary flow reserve and attempt to correlate this with angina. In the most part we get it right, but there is less certainty about the prognostic significance of a lesion. Why does a young man have his life ruined or ended by a 30% narrowing in one coronary artery causing myocardial infarction and another 85 year old patient present with severe but stable angina, multiple coronary artery occlusions, and preserved left ventricular function? Ruptured atherosclerotic plaques are seen at necropsy in some patients who have died of non-cardiac causes, and presumably, therefore, the healing of silent ruptures is to some extent normal. Patients who have a myocardial infarction are for some reason unable to heal that plaque rupture, at that moment, at that particular site. But why? The answers are presumably in the genetic make up of the patient, the biology of the plaque causing the luminal narrowing, and the nature of the patient's platelets and coagulation system. How does modern biology help?

Genetic risk

Atherosclerosis has an inflammatory component, and many aspects of an individual's inflammatory response

Modes of presentation of ischaemic heart disease: are these determined genetically?

Sudden ischaemic coronary death
Acute myocardial infarction
Unstable angina
Chronic coronary insufficiency
Left ventricular failure

are genetically programmed.² The plaque contains monocytes, macrophages, and T lymphocytes and is rich in several inflammatory cytokines. Patients with unstable angina who have an unfavourable outcome are characterised by a systemic inflammatory response.^{2,3} The inflammatory response in any individual is programmed by their genetic composition,⁴ and such genetic variation may influence the course of disease—for example, polymorphisms in tumour necrosis factor α predict the development of cerebral malaria.⁵

Ischaemic heart disease runs in families, but only some of the inherited risk is explicable by known genetic determinants of lipid metabolism or of coagulation. Therefore, many other genes are probably important in either the pathological process itself or in the mode of presentation. The genetic determinants of the inflammatory response and of platelet function are examples of this that are currently attracting attention and may be particularly important in determining the mode of presentation and course of ischaemic heart disease (box). These are called disease modifying genes—that is, they do not cause the disease but affect the disease process and are highly relevant to our clinical problems.

Identification of the disease modifying genes is not far off. How is it being done? Large databases of well characterised patients and their genomic DNA will allow the association of particular alleles of (candidate) genes with a particular type of presentation. This is followed by prospective studies of people with the identified genetic risk and matched in parallel with linkage studies in families with a history of premature coronary disease. Eventually the entire genetic risk of developing coronary disease and the likely mode of presentation will be described by such analysis. As well as providing new markers of disease that will allow genetic screening programmes, and thus modification of risk factors, new targets for drugs and ways of treatment will emerge.

Plaque biology

Totally stable, unrupturable plaques must differ from those that rupture. What makes a plaque stable? Plaque stability is favoured by strong caps and shoulder regions, perhaps rich in smooth muscle cells and having an intact overlying endothelium. Stability would be favoured by an environment of a quiescent endothelial cell layer covering a stable population of smooth muscle cells, along with a population of quiescent healthy macrophages with a small lipid core. The fundamental biological research currently being undertaken enhances our prospects of creating this plaque environment.

Cell biologists are examining the characteristics of plaques and defining the conditions that favour instability. The basic science approach is then applied.

Fig 1 Possible methods for testing treatments to improve plaque stability and their introduction into humans. (Methods given in parenthesis)

Modern techniques are used to determine the exact consequences of the observed changes on the cells of the vessel wall. This then allows a number of targets to be identified which if either removed or in some cases overexpressed will favour plaque stability. These can then be tested in animals to prove the hypothesis and then taken into humans (fig 1).

This type of work is going on throughout the world and is at different stages. The beneficial effects of aspirin and statins has convinced us that plaque pacification therapy is possible, but coronary care units remain full despite this. On the visible horizon are drugs directed against the platelet integrin II_b III_a.⁷ These have shown great promise in percutaneous transluminal angioplasty and are now being tested in unstable angina and prospectively in patients with ischaemic heart disease.

Can we eliminate restenosis after percutaneous transluminal angioplasty?

With the development of interventional cardiology a new disease was born—coronary restenosis. This term is used when a patient who has had a flow limiting stenosis in their coronary artery treated by percutaneous transluminal angioplasty has a short respite from angina before the narrowing recurs leading to the return of angina. About 30-50% of patients develop restenosis within six months after angioplasty, and the rates of restenosis after insertion of a coronary stent are contested but around 10-30%.^{8,9} These techniques cannot, therefore, be regarded as highly satisfactory. Cardiologists are as a result looking to basic science to solve the problem of restenosis. The solution, when found, will undoubtedly change the treatment for all patients with ischaemic heart disease.

Angioplasty triggers a healing response

Percutaneous transluminal angioplasty causes splitting of the vessel at the shoulder of the plaque. The blood vessel has a well defined response to injury (box) and

Coronary artery response to injury: which one to target?

Elastic recoil
Thrombus formation
Inflammatory cell influx
Proliferation (and apoptosis) of vascular smooth muscle cells
Migration of smooth muscle cells
De-differentiation of vascular smooth muscle cells
Differentiation of fibroblasts
Extracellular matrix protein production
Arterial shrinkage/remodelling

heals in a predictable manner,¹⁰ though this is modified by stent implantation (fig 2). This has several implications. Firstly, technological developments such as atherectomy catheters (cutters and borers) or lasers (burners) which produce the same responses to injury are associated with the same restenosis rates.^{11 12} Secondly, restenosis arises from a normal tissue response since its pathogenesis is a healing reaction. Detailed angiographic studies of patients after angioplasty show that the degree of luminal diameter loss six months after dilatation is normally distributed and those that suffer from angina are simply at one end of the Gaussian curve. Investigation into new treatment must dissect the mechanisms of the process and examine whether there are patient characteristics that favour a more exuberant healing response. Furthermore, any treatment must preserve the healing response to some degree as complete abolition will produce an unfavourable outcome.

The understanding of the biological response to injury of the vessel wall has been advanced by the study of animal models of percutaneous transluminal angioplasty, which include the porcine coronary artery (fig 2). The mechanisms of this response are outlined in the box. Although manipulation of one of these factors in laboratory animals has often reduced the vascular response, the same treatments have generally not reduced clinical restenosis in humans. For example, angiotensin converting enzyme inhibitors reduced neo-intima formation after balloon injury in animals¹³

Fig 2 Porcine coronary artery treated by balloon angioplasty. The kidney shaped lumen results from growth of material which is part of healing reaction at the site of arterial splitting during the procedure and this eccentrically narrows the lumen. (Bottom) Porcine coronary artery which has been stented. The response to injury is an eccentric neointima, which may sometimes be large enough to reduce luminal diameter sufficiently to limit coronary flow. Both sections were taken 28 days after the procedure and stained with haematoxylin and eosin

Fig 3 Basic science strategy to investigate treatment to prevent coronary restenosis. (Methods given in parenthesis)

but had no benefit in humans.¹⁴ The reasons for this are likely to be multitudinous. As usual a more complete understanding of the biological basis of the problem is required. How might this be obtained?

Scientific strategy to solve the problem of restenosis

Molecular cell biologists have many tools to dissect the vascular response to injury. With no more than milligram amounts of material from both normal segments of vessels and restenotic lesions they can now explore differences in gene expression. Figure 3 shows a strategy for how a programme of basic science might help yield the complete picture. One of the tools mentioned is differential display polymerase chain reaction¹⁵ and shows the power of these molecular biological techniques. This method allows comparison of a large number of the genes being expressed in two cells or tissues by analysing the different mRNAs. The approach produces a genetic signature of a cell or tissue under a specific set of circumstances. Partial cDNA sequences from the subsets of mRNA are systematically amplified and separated by size on a DNA sequencing gel. The banding pattern allows side by side comparison of nearly all the mRNAs in the different cell types or tissues.

As alluded to above, the function of a gene within an individual may be determined by a polymorphism within that gene. Novel disease associated genes identified above can be investigated for polymorphisms by new techniques such as single strand conformational polymorphism analysis.¹⁶ This technique identifies sequence changes in amplified DNA. The method is based on the observation that the mobility of single

stranded DNA in particular gel matrices is very sensitive to the primary DNA sequence (slight sequence changes have major effects on conformation). Once a polymorphism is identified the effect of over expression of the protein products of the different alleles in cell in culture is examined. If a biologically relevant difference in response is noted genomic DNA banks from well characterised patients who have had angioplasty are screened using the identified polymorphic gene and thus susceptibility genes for restenosis are identified. These patients are then sent for bypass surgery. Fantasy? You wait.

How can more donor organs be made available for cardiac transplantation?

Heart failure is the end point of coronary disease and has a terrible prognosis. Cardiac transplantation has improved not only symptoms but prognosis in such patients. But transplants are available to only a few of the affected patients because of a shortage of organs. In Western cultures millions of animals are slaughtered each year for food, and as a result scientists have begun to examine the possibility of transplanting pig hearts into humans (xenotransplantation).

Xenotransplantation has been hampered by hyperacute rejection

Leaving aside the ethical and moral issues, xenotransplantation has many immunological difficulties.¹⁷ In transplantation between individuals of the same species rejection is based on an antibody attack of different class I and II major histocompatibility complex antigens in the graft (donor) by the recipient. However, transplantation across phylogenetically different species produces a rapid response called hyperacute rejection. This usually causes thrombosis and death of the transplanted organ within minutes because of the presence of natural antibodies to other species. These antibodies bind to a sugar molecule on the surface of non-primate endothelial cells and activate the complement pathway. Endothelial cells also possess natural inhibitors of the complement pathway including decay accelerating factor (DAF, CD55), membrane cofactor protein (MCP, CD46), and membrane inhibitor of reactive lysis (CD59). These are, however, species specific. So when a pig heart is grafted into a human the human xenoreactive antibodies bind the porcine sugar molecule on the endothelium of the graft and activate human serum complement, but the human complement is not inhibited by the porcine inhibitors of activation.

Transgenic animals may be the answer

To overcome this problem scientists have tried to breed pigs that express one of the genes for human complement inhibitors in their endothelium—and with some success. Genetically engineered pigs containing the gene for human decay accelerating factor and other related inhibitors have been made and bred. Hearts from these pigs have been grafted into other primates, and their survival is extended from minutes to days.¹⁸ Considerable difficulties persist. Both high level and continued expression of human decay accelerating factor needs to be ensured. It would be advantageous to remove the sugar molecules from the surface of pig cells,

but gene knockouts are currently feasible only in mice. (Knocking out genes is proving more difficult than additional expression of genes.) These technical matters are bound to be solved by the seemingly unending ingenuity of the transgenic scientists. Undoubtedly, as they are solved more immunological problems will be encountered (after all every cell surface protein will potentially be immunologically different) but development of immunosuppressive agents is likely to continue and help solve these difficulties.

Conclusion

Basic science is being applied to the major problems arising from ischaemic heart disease. In the next decades the management of patients with ischaemic heart disease will be changed by these developments and our treatment of this plague of the Western world will look quite different. Plaques will be rendered quiescent, luminal narrowings removed never to return, and patients with heart failure will get new hearts. We have to encourage and promote these advances to ensure that any delay in these breakthroughs cannot be ascribed to us.

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- 1 Compendium of health statistics. 9th ed. London: Office of Health Economics, 1995.
- 2 Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, *et al*. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med* 1994;331:417-24.
- 3 Maseri A, Biasucci LM, Liuzzo G. Inflammation in ischaemic heart disease. *BMJ* 1996;312:1049-50.
- 4 Duff GW. Molecular genetics of cytokines. In: Thomson A, ed. *The cytokine handbook*. 2nd ed. London: Academic Press, 1994:21-31.
- 5 McGuire W, Hill AV, Allsopp CE, Greenwood BM, Kwiatkowski D. Variation in the TNF-alpha promoter region associated with susceptibility to cerebral malaria. *Nature* 1994;371:508-10.
- 6 Savill J. Molecular genetic approaches to understanding disease. *BMJ* 1994;314:126-9.
- 7 Lefkowitz J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. *N Engl J Med* 1995;332:1553-9.
- 8 Fishman DL, Leon M, Baim DS, Schatz RA, Savage MP, Penn I, *et al*. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;331:496-501.
- 9 Serruys PW, de Jaeger P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, *et al* for the Benestent Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary disease. *N Engl J Med* 1994;331:489-95.
- 10 Hamon M, Bauters C, McFadden EP, Wernert N, Lablanche JM, Dupuis B, *et al*. Restenosis after coronary angioplasty. *Eur Heart J* 1995;16(suppl 1):33-48.
- 11 Appelman YE, Piek JJ, Strikwerda S, Tjissen JG, de Feyter PJ, David GK, *et al*. Randomised trial of excimer laser angioplasty versus balloon angioplasty for treatment of obstructive coronary disease. *Lancet* 1996;347:79-84.
- 12 Topol EJ, Leya F, Pinkerton CA, Whitlow PL, Hoffing B, Simonton CA, *et al*. A comparison of directional atherectomy with coronary angioplasty in patients with coronary disease. The CAVEAT Study Group. *N Engl J Med* 1993;329:221-7.
- 13 Powell JS, Clozel J-P, Muller RKM, Kuhn H, Hefti F, Hosang M, *et al*. Inhibitors of angiotensin-converting enzyme prevent myointimal proliferation after vascular injury. *Science* 1989;245:186-8.
- 14 Multicentre European Research Trial with Cilazapril after Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (Mercator) Study Group. Does the new angiotensin-converting enzyme inhibitor cilazapril prevent restenosis after percutaneous transluminal angioplasty? Results of the Mercator study: a multicentre, double-blind, placebo-controlled trial with cilazapril. *Circulation* 1992;86:100-10.
- 15 Wang X, Ruffolo RR, Feurstein GZ. mRNA differential display: application in the discovery of novel pharmacological targets. *Trends in Pharmac Sci* 1996;17:276-9.
- 16 Orita M, Suzuki Y, Sekiya T, Hayashi K. Rapid and sensitive detection of point mutations and DNA polymorphisms using polymerase chain reaction. *Genomics* 1996;5:874-9.
- 17 Warrens AN, Dorling A, Lechler RI. The prospects for xenotransplantation. *Q J Med* 1996;89:885-91.
- 18 McCurry KR, Kooyman DL, Alvarado CG, Cotterell AH, Martin MJ, Logan J, *et al*. Human complement regulatory proteins protect swine to primate xenografts from humoral injury. *Nature Medicine* 1995;1:423-7.