

CARDIOVASCULAR RESEARCH FUNDERS FORUM

Heart failure: aetiology, diagnosis, and treatment

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A two day meeting on heart failure, organised by the Cardiovascular Research Funders Forum, took place at the Royal College of Physicians, London, earlier this year. The meeting brought together over 60 researchers from the UK, North America, and continental Europe, representing basic and molecular scientists and clinicians (cardiologists, surgeons, and nurses) plus patient representatives

Many aspects of the opening session (which set the scene for the meeting) will be familiar to those practising in cardiology. Philip Poole Wilson (London) reflected that heart failure had for many years been a Cinderella subject, but that much had been learned about its aetiology and pathophysiology, which in 80% of instances is caused by loss of heart muscle. He believed that the headline data on epidemiology were already available, a view challenged by Martin Cowie (London), particularly in respect of diastolic heart failure. There was, however, agreement concerning prognosis, which is especially bad in the year following first diagnosis (37%) and with a further 10% mortality in each subsequent year.

Martin Cowie drew attention to the increasing burden on the National Health Service: heart failure now accounts for 5% of all acute medical admissions in the UK and 10% of bed days. There is a need for greater emphasis on prevention, especially in those with pre-existing coronary heart disease (CHD) and those who are at high risk of developing it, a theme developed by David Wood (London). He defined prevention as either delaying the development of clinical heart failure or preventing its occurrence completely. Strategies for prevention include systematic screening for left ventricular dysfunction and/or selective screening of patients with a diagnosis of cardiovascular disease (CHD, peripheral vascular disease or stroke) and those with diabetes mellitus. Potential opportunities for prevention exist in patients with angina, many of whom have well preserved left ventricular function. Current shortcomings include inadequate documentation of

blood pressure and its poor control. Finally, there are major opportunities for screening first degree relatives of those who develop CHD at a young age since many may have a genetic predisposition.

DIAGNOSIS

The problems of diagnosis, particularly within the setting of UK general practice, were rehearsed by Richard Hobbs (Birmingham). Echocardiography is the gold standard diagnostic technique, but there are insufficient slots available to general practitioners in most parts in the UK. Furthermore, once diagnosed, heart failure is inadequately managed, as many general practitioners fear that angiotensin converting enzyme inhibitors will cause adverse effects such as hypotension and renal failure. The use of natriuretic peptides, especially brain natriuretic peptide (BNP) was reviewed by Allan Struthers (Dundee). He identified four potential uses (box 1). The screening of asymptomatic patients has merit in view of the fact that those with borderline abnormalities of left ventricular function have a poor prognosis. In those with symptoms, BNP has a sensitivity of 97% with specificity of 84%. More importantly, a normal value of BNP has a negative prediction value of 98%. The potential value of BNP in assessing prognosis is considerable and the analogy was drawn with glycosylated haemoglobin used by diabetologists (BNP concentrations are a composite reflection of cardiac structural disease and renal function). Thus, in future, BNP may be used as a guide to the efficacy of treatment.

AETIOLOGY

On the first day of the conference, Bill McKenna (London), focused on genetic factors in dilated cardiomyopathy (DCM). At least 20% of familial cases of DCM have associated atrial ventricular conduction block and organ specific cardiac autoantibodies are present in 26–44%. To date, gene mutations have been identified in 10 cardiac proteins. By contrast, Desmond Sheridan (London) concentrated on hypertension as a cause of heart failure. Although hypertension alone may be responsible for about a quarter of all cases of heart failure, in combination with other problems such as ischaemic heart disease, it can be implicated in three quarters. The ECG is an

Box 1: Uses of natriuretic peptides

- Screen asymptomatic patients for left ventricular systolic dysfunction and left ventricular hypertrophy
- Diagnose heart failure in symptomatic patients
- Assess prognosis in known cases
- Monitor treatment in known cases

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Abbreviations: BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CHD, coronary heart disease; CHF, congestive heart failure; DCM, dilated cardiomyopathy; LVH, left ventricular hypertrophy; LVAD, left ventricular assist device

insensitive measure of left ventricular hypertrophy (LVH), but if present is associated with a six-fold increase in risk of death from myocardial infarction. Echocardiography is more sensitive and provides a good means of following regression with treatment. Antihypertensive treatment causes a regression of LVH but, despite claims of greater benefits arising from treatment with ACE inhibitors or diuretics, no single therapeutic class stands out as being the most effective. Professor Sheridan suggested that long term (24 hour) blood pressure reduction was the dominant mechanism underlying benefit.

John McMurray (Glasgow) drew attention to three other risk factors: atrial fibrillation, smoking, and diabetes. Diabetes is present in a quarter to a third of patients with congestive heart failure (CHF) and about half of patients with a low ejection fraction have abnormal glucose or insulin metabolism. Furthermore, diabetes increases the risk of CHF after myocardial infarction. However, much remains to be resolved about the mechanisms by which these risks are interlinked and result in the development of CHF.

The remainder of the day focused on myocyte cellular changes. Peter Sugden (London) reminded us that myocytes are terminally differentiated. Growth is adaptive and responsive to haemodynamic loads. Furthermore, because myocytes are incapable of cell division, the myocardium is particularly susceptible to loss—for example, after myocardial infarction. Hypertrophy of myocytes is accompanied by increased protein content and myofibrillogenesis with the expression of several genes and BNP. These changes are mediated by stimulation of transmembrane receptors with subsequent intracellular signalling involving protein kinase C and mitogen activated kinases, with subsequent effects on calcineurin and other calcium dependent pathways. Although initially cardiac hypertrophy is a beneficial adaptation, in the longer term the heart may decompensate and fail for reasons which are as yet obscure. These include hypoxia, free radical formation, activation of pro-apoptotic signalling pathways, and myocardial necrosis with subsequent fibrosis.

Sian Harding (London) emphasised the abnormalities of calcium cycling which occur in failing cardiomyocytes, resulting in prolonged beat duration and poor cellular relaxation. These alterations are potentially reversible with the use of left ventricular assist devices (LVADs) and are matched by altered expression of SERCA2a. In addition β adrenoceptor desensitisation occurs in human ventricular myocytes and this is accompanied by reduced cyclic AMP concentrations. These features are independent of the aetiology of CHF and can be reversed by LVADs.

David Eisner (Manchester) provided further details of changes in calcium handling in the failing myocyte. The calcium content of the sarcoplasmic reticulum is a powerful determinant of systolic calcium concentrations, but it is possible to overload the cell thereby producing subsequent spontaneous overload and arrhythmias. Experimentally, some of these changes can be reversed with tetracaine and the search is on for more specific agents.

Stephan Neubauer (Oxford) focused on cardiac energy metabolism in heart failure and outlined the potential mechanisms by which contractile function could be reduced (box 2). In experimental models he illustrated the reduced ATP transfer, and decreased mitochondrial size and function.

The final contribution of the first day of the conference came from Roberto Ferrari (Ferrara, Italy) and was on stunning, hibernation, and remodelling. Hibernation is defined as a dysfunction which is reversible and occurs during ischaemia, and can be identified by means of positron emission tomography, thallium scanning or by stress echocardiography during low dose dobutamine. These imaging techniques allow the identification of individuals suitable for surgery which can result in an improved ejection fraction and other measures of left ventricular function. Despite a significant perioperative mortality rate of up to 20%, three

Box 2: Energy metabolism of heart failure—potential mechanisms limiting contractile function

- ATP content
- ATP turnover and delivery
- Free energy change of ATP hydrolysis
- Mitochondrial function
- Substrate availability

years survival is excellent. By contrast, myocardial stunning is a transient episode of left ventricular dysfunction which persists after reperfusion and may therefore occur after successful thrombolytic treatment or revascularisation procedures. The potential mechanisms underlying stunning are numerous and are a reflection of our current lack of knowledge.

TREATMENT

The second day the conference focused on newer aspects of treatment for heart failure. Philippe Menasche (Paris) described the results of skeletal myoblast transfer in man. Based upon previous studies in animals, they had been able to optimise cell survival of thigh muscle myoblasts grown in culture. After 16 days' culture a suspension containing 150×10^6 cells/ml is injected into scar tissue at the time of coronary artery bypass graft surgery (CABG). Although some 90% of these cells die early after transplantation, those that survive remain committed to skeletal muscle form, but are resistant to ischaemia. To date, there is no evidence that skeletal myoblast transplantation leads to the formation of connexin 43 junctions, but arrhythmias remain a potential complication. Nevertheless, initial results in eight patients have shown evidence of improved cardiac function. A trial is proposed which will compare CABG grafting and injection of medium with CABG surgery and transplanted cells in 70–75 patients.

Ken Suzuki (Harefield) reviewed the possible targets for gene therapy, including the induction of angiogenesis and attempts to improve cardiac contractility or to modify adverse remodelling. Many issues remain to be resolved including the limited efficiency and potential toxicity arising from an inflammatory response and involvement of distant organs. Uncertainty exists as to the best methods of delivery. Vectors include naked plasmid, liposomes or adenoviruses given by means of direct injection via intracoronary or intrapericardial routes. He showed that liposomal delivery of the VEGF gene could reduce infarct size as well as improving cardiac function in experimental myocardial infarction. VEGF-myoblast gene therapy led to regeneration of myotubules and improved angiogenesis.

Subsequently, Bodo Strauer (Dusseldorf, Germany) reviewed the studies relating to stem cell transfer in coronary artery disease in man. He was followed by Christine Mummery (Netherlands Institute for Developmental Biology). Her presentation covered the definition and biology of embryonic stem cells based on work carried out in mice. Embryonic stem cells resemble teratocarcinoma cells and can grow indefinitely in culture and retain pluripotency. Differentiation into cardiomyocytes can be encouraged by co-culture with visceral endoderm-like cell lines. However, the capacity to differentiate into cardiomyocytes is variable and currently relatively inefficient. Thus, transplantation of embryonic stem cell derived cardiomyocytes in man is "way off". Nevertheless, the clear distinctions between embryonic stem cells and those derived from skeletal muscle make it important for this avenue of research to be supported.

Michael Schneider (Houston, USA) educated the conference on the factors controlling cell growth and division as well as the cascades which eventually result in cell death. He demonstrated a major inhibitory role for p21 in cardiac apoptosis. In addition, he illustrated the importance of telomeres,

specialised DNA-protein structures that cap linear chromosomal endings. During DNA replication telomere repeats are maintained by TERT—an RNA dependent DNA polymerase. TERT has the capacity to rescue telomerase activity, and even in the adult heart can induce an hypercellular myocardium and cardiac hypertrophy as well as inhibiting cardiac apoptosis.

John Cleland (Hull) reviewed the role of multi-site pacing and implantable defibrillators in heart failure. In theory, multi-site pacing can resynchronise cardiac activity, thereby improving efficiency and reducing morbidity and mortality. The MIRACLE trial, which involved 266 patients, led to improvement in symptoms in 63% when the pacing was on compared with 38% when the pacemaker was switched off. Although these and other results are promising, resynchronisation therapy is unlikely to benefit more than a quarter of all people admitted with heart failure and to date there is little information on mortality. Implantable cardioverter defibrillators have been advocated because approximately half of all deaths in patients with heart failure are “sudden” and thought to be caused by an arrhythmia. However, the only definite indication for their implantation is resuscitated sudden arrhythmic death.

John Wallwork (Papworth) reminded us of the biology and preclinical testing of xenotransplants. These have been well worked out and transplantation of pig xenografts has taken place in baboons, which have survived up to six months. However, to date humans have been denied this approach because of the possible transmission of pig viruses to man. It is, therefore, unclear as to when, if ever, this technology might be available to treat patients. By contrast, long term left ventricular assist devices have been employed in the UK as demonstrated by Stephen Westaby (Oxford) who described the various devices which are available and focused on the Jarvik 2000 heart. After describing the surgical technique he reviewed the results in four patients, the first of whom was present for most of the conference. Together with input from the British Cardiac Patients Association he kept the researchers’ feet firmly on the ground. However, it is clear that there is a need for carefully controlled clinical trials of such LVADs.

Box 3: Key components of the Glasgow Heart Failure Liaison Nurse Service

- Ongoing assessment, education, and support
- Regular review of medication
- Adjustment and optimisation of therapy
- Close monitoring of blood chemistry
- Facilitates self management
- Act as an intermediary
- Patient held information book
- Ease of access to the service
- Emotional support

The patient and his/her experience was also the focus of the presentation by Lynda Blue from the Glasgow Heart Failure Liaison Nurse Service. This provides individualised care and monitoring for patients admitted to hospital with heart failure. Key components of the service are identified in box 3.

CONFERENCE SUMMARY

The conference ended with a summary by Sir George Radda, chief executive, Medical Research Council. He concluded that heart failure is a multivariant disease and that the variables are interactive. We need to understand how the various interactions contribute to the final course of heart failure. He emphasised the importance of using new techniques such as those for detecting changes in activity/expression of genes within the cell when certain cellular/genetic events occur. Cardiovascular researchers have lagged behind those studying cancer in exploiting the possibilities of such techniques. Similarly, they have made limited use of more simple model systems than their counterparts. Recent legislation in the UK gives us an opportunity to gain a better understanding of influencing the development of embryonic stem cells. However, it is important not to misuse public confidence by moving faster than our knowledge of biology allows. He urged those present to place more emphasis on how to move from basic biology into the clinic and of exploiting population genetic techniques, drawing attention to the potential value of studying isolated populations such as those in Iceland and on the population at large as proposed in the BioBank UK initiative. Despite these limitations, the conference succeeded in bringing together people from disparate disciplines and in building useful networks.

APPENDIX

The Cardiovascular Research Funders Forum (CVRFF) is composed of the major cardiovascular research funders who meet on a bi-annual basis to:

- consider issues of mutual interest relating to cardiovascular disease
- looked at how best to plan and share research expertise
- help improve strategic coordination of research.

The current membership of the CVRFF is:

- The British Heart Foundation
- Diabetes UK
- Medical Research Council
- The Wellcome Trust
- Department of Health
- Scottish Executive Health Department
- Welsh Office of R&D of Health and Social Care
- Northern Ireland Department of Health, Social Services & Public Safety.