New perspectives on heart failure due to myocardial ischaemia


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Introduction

Heart failure is a leading cause of morbidity and mortality in the community[1]. Despite improvements in the treatment of heart failure in recent years, for example the use of angiotensin converting enzyme (ACE) inhibitor therapy, morbidity, mortality and resource consumption remain high. In the U.K. heart failure absorbs 1% of the National Health Service budget[2].

Current evidence from developed countries suggests ischaemic heart disease is the dominant aetiological factor in the increasing burden of heart failure[3,4]. Recent work has demonstrated that myocardial dysfunction due to ischaemia is a dynamic and, at least in part, a reversible process[5]. Techniques to detect potential reversibility in individual patients, combined with treatment directed against the ischaemia rather than the contractile dysfunction may provide new approaches to the management of this syndrome.

Epidemiology

The epidemiology of heart failure has recently been reviewed[4]. The crude incidence (unadjusted for age) in communities in developed countries ranges from 1·0–5·0 cases per 1000 population per annum. A recent population survey in Hillingdon, West London, using strict diagnostic criteria, estimated the incidence of heart failure to be 0·8 cases per 1000 population per annum[6], with a marked and progressive increase in incidence with age from 0·2 cases per 1000 population per annum aged 35–44 years to 11·6 cases per 1000 population per annum aged over 85.

The proportion of patients with heart failure due to coronary heart disease varies substantially between studies. Evidence for coronary heart disease can be based on the patient’s history without objective evidence of coronary artery disease or on a validated history of myocardial infarction. The latter could underestimate the role of coronary heart disease when used in retrospective studies. Electrocardiogram (ECG) findings, using the presence of Q waves or left bundle branch block will detect silent infarcts but will underestimate the presence of coronary artery disease. Q waves may not be due to infarction. Coronary angiography will identify those patients in whom coronary artery disease is present. However, to determine that coronary artery disease is the cause of myocardial dysfunction may require further evidence. Coronary artery disease is clearly implicated where a blocked vessel subtends a regional infarct, but in other cases where a modest coronary stenosis subtends an area of resting contractile dysfunction the causative nature of the association cannot be proven. Imaging involving echocardiography, magnetic resonance imaging or nuclear techniques may be needed in an attempt to demonstrate a causative and dynamic relationship between coronary artery disease, myocardial dysfunction and heart failure.

The Framingham study, a prospective study using biennial history, examination and ECG recordings, found evidence of coronary artery disease (non-invasively) in 42% of men and 25% of women predating heart failure[7].

However, the proportion of heart failure cases due to coronary heart disease is greater in other, particularly more recent, studies using different methodologies. A surveillance study in Eastern Finland, using non-invasive data, reported coronary artery disease as the aetiology in 61% of cases of heart failure.
Mechanisms of myocardial dysfunction due to ischaemic heart disease

In recent years our understanding of the variety of mechanisms whereby ischaemia affects the myocardium has expanded. The list now includes irreversible infarction, acute ischaemia, reversible stunning, hibernation and protective preconditioning (Table 1). Central to our current understanding is that myocardial dysfunction due to stunning and hibernation implies a potential return to normal function if the ischaemia is resolved (i.e. the myocardium is viable).

Heart failure resulting from ventricular dysfunction has many elements. In addition to myocyte dysfunction, there may be changes in the ventricular matrix, with collagen deposition and scarring together with changes in cavity size and shape (remodelling). Diastolic, in addition to systolic, dysfunction can result in the clinical syndrome of heart failure. Coronary artery disease syndromes affect all these aspects of ventricular function.

Complete occlusion of the blood supply to an area of myocardium leads to cell necrosis starting after 20 min[12]. Areas of necrosis cannot regain contractile function. Subsequent scar formation and ventricular remodelling may, over time, impact further on overall ventricular function. Acute myocardial infarction is therefore an important mechanism for the development of heart failure, both at the time of infarction, as well as over the ensuing months and years. Although there is no convincing evidence from population studies that the prognosis of myocardial infarction has improved, clinical trials in selected patients suggest this may be the case[13], together with evidence that newer treatments (thrombolysis) are effective in a population setting[14]. Assuming that there is an increased incidence of heart failure, then the improved prognosis for myocardial infarction would be the most important reason, since it leaves patients at risk of the development of heart failure.

During periods of acute ischaemia the contractile function of the ventricle declines[15]. Proposed mechanisms centre around a rise in inorganic phosphate following ischaemia-induced ATP and creatine phosphate breakdown[16]. This occurs both with overt and silent ischaemic episodes[17]. Although contractile function returns to normal when ischaemia resolves, and despite some recent work demonstrating left ventricular function can remain stable in patients with stable angina[18], recurrent ischaemic episodes, overt or silent, may have a long term detrimental effect on contractility[5].

Myocardial stunning describes the process of post-ischaemic transient myocardial dysfunction. First described by Heyndrickx et al[19], stunning is seen in many situations including after percutaneous transluminal coronary angioplasty (PTCA) [20], and in cases of unstable angina[21]. The ischaemia is insufficient to cause necrosis (i.e. lasts less than 20 min in most cases) and under such conditions myocardial dysfunction resolves completely with time[22]. While the mechanisms of stunning are incompletely understood free radical production and an increase in cytosolic calcium seem important to the process[23]. Stunning is important, not only as a cause of transient left ventricular dysfunction but also because of evidence suggesting that repeated stunning may lead to hibernation[24].

The concept of the hibernating myocardium was first introduced by Rahimtoola[25,26]. In hibernation left ventricular systolic function is persistently but reversibly impaired due to reduced coronary flow. Hibernation may be considered an adaptive response of ischaemic myocardium, avoiding cell death at the expense of contractile function. Hibernation covers a spectrum of changes from totally reversible myocyte dysfunction without cell matrix changes to only partially reversible dysfunction with histologically visible changes in the matrix and myocyte. Alterations in perfusion cause shifts along the spectrum and in particular, if perfusion declines sufficiently, cell necrosis and scar formation will take place. Clinical evidence for hibernation, by demonstrating live but non-contractile myocytes has accumulated in recent years[27]. The exact mechanism is unclear and no single mechanism is likely to explain the full spectrum of effects. Many elements including altered metabolism (oxidative and calcium handling) as well as structural changes (downgraded myofibrils) are involved[28].

In contrast to the impaired but potentially reversible dysfunction seen with stunning and hibernation, ischaemic preconditioning is a process whereby the myocardium, after exposure to a period of ischaemia, develops resistance to further ischaemic insults[29]. Evidence for preconditioning in isolated human heart tissue has been found[30] and clinical evidence for preconditioning also exists[31]. Proposed mechanisms of preconditioning centre around adenosine, perhaps linked to ATP-sensitive potassium channels, with other
### Table 1 Features of the various mechanisms whereby ischaemia affects the myocardium

<table>
<thead>
<tr>
<th>Ischaemic mechanism</th>
<th>Normal</th>
<th>Acute ischaemia</th>
<th>Infarction</th>
<th>Acute stunning</th>
<th>Hibernating</th>
<th>Ischaemic preconditioning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood supply</strong></td>
<td>Normal</td>
<td>Reduced</td>
<td>Episode of prolonged occlusion</td>
<td>Transient prior reduction then restoration</td>
<td>Chronic reduction, may be modest at rest but repetitively reduced under stress</td>
<td>Recurrent brief episodic reduction</td>
</tr>
<tr>
<td><strong>Resting contractile function</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Nil</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Function under stress</strong></td>
<td>Normal</td>
<td>Impaired</td>
<td>Nil</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Preserved</td>
</tr>
<tr>
<td><strong>Metabolic activity (PET scanning)</strong></td>
<td>Normal</td>
<td>Reduced</td>
<td>Nil</td>
<td>—</td>
<td>Reduced but may improve with delayed reinjection techniques + nitrates</td>
<td>—</td>
</tr>
<tr>
<td><strong>Echo features with dobutamine stress</strong></td>
<td>Normal</td>
<td>Impaired contractility with high dose dobutamine</td>
<td>No contraction</td>
<td>—</td>
<td>Some transient improvement in contractility at low doses</td>
<td>—</td>
</tr>
<tr>
<td><strong>Histological features</strong></td>
<td>Normal</td>
<td>—</td>
<td>Scarring and fibrosis</td>
<td>May be normal histologically</td>
<td>Spectrum from myofibril loss to cell matrix changes and scarring</td>
<td>—</td>
</tr>
<tr>
<td><strong>Biochemical features</strong></td>
<td>Normal</td>
<td>Rise in inorganic PO4 and adenosine from ATP breakdown seen during ischaemia</td>
<td>Nil or minimal metabolic activity</td>
<td>Increased cytosolic calcium</td>
<td>Downregulated ATP demand</td>
<td>Reduced ATP demand under stress protein C activated</td>
</tr>
<tr>
<td><strong>Response to further ischaemia</strong></td>
<td>—</td>
<td>May proceed to infarction (or one of the other syndromes)</td>
<td>—</td>
<td>May become hibernating</td>
<td>Eventually proceeds to infarction</td>
<td>Decreased infarct size</td>
</tr>
<tr>
<td><strong>Response to revascularization</strong></td>
<td>—</td>
<td>Normalized</td>
<td>No effect</td>
<td>Normal</td>
<td>Potential full or partial recovery</td>
<td>Normal</td>
</tr>
</tbody>
</table>

...ion channels and metabolic enzyme changes also involved\(^{[30]}\). Preservation of ATP after the early ischaemic episodes occurs and may provide metabolic protection at later times. As with all the above mentioned effects of ischaemia on the myocardium, much remains to be learnt about the clinical importance of preconditioning.

These mechanisms for ischaemic alterations to the myocardium have all been described separately, but they interlink, representing a range of changes depending on the particular alteration in perfusion and the response of the myocardium. Variations across the range can occur not only in different individuals, but within an individual heart\(^{[5]}\). It is possible for a patient on a cardiac ward following myocardial infarction to have an area of irreversible infarction surrounded by stunned myocardium in the peri-infarct zone with hibernating myocardium distal to the same or other coronary stenoses. Previous ischaemic episodes may precondition parts of the myocardium while further ischaemic episodes, at rest or on exertion, may add to contractile impairment.

The overall cardiac function will be a complex sum of these elements. However the extent to which this diversity exists in practice, and the level at which variation can occur, from myocyte to the territory of an epicardial coronary artery or the whole heart remains ill defined. To assume myocardium is simply dead or alive is an oversimplification. Similarly it would be naïve to assume coronary artery disease in an individual leads either to painful angina or silent progressive dysfunction but not both. The idea of a complex middle ground of viable, impaired but most importantly reversible, ischaemic myocardium, seems on current evidence, to be both scientifically plausible and clinically demonstrable.

**Detecting hibernating myocardium**

The demonstration of active metabolism combined with impaired function in an area of myocardium distal to a coronary stenosis is necessary. The current gold standard for the detection of hibernation is positron emission tomography scanning\(^{[32]}\). Positron emission tomography scanning detects the increased glucose utilization relative to perfusion seen in hibernating myocardium. Unfortunately this highly sensitive technique is expensive and available in only a few centres. Other isotope imaging methods have been developed employing Thallium 201 and Technetium 99 containing tracers\(^{[33]}\). These circulate to areas of the heart, depending on perfusion and the presence of metabolically active myocardium. Images are matched to wall motion abnormalities seen on echocardiography or ventriculography to identify hibernating myocardium.

Dobutamine stress echocardiography, a technique widely available, can also be used to identify viable myocardium\(^{[34]}\). Low doses of dobutamine (up to 10 μg \(\cdot\) kg\(^{-1}\) \(\cdot\) min\(^{-1}\)) recruit viable myocardium improving wall motion before higher doses produce a reduction in wall motion in ischaemic areas. Magnetic resonance imaging techniques have also been developed to detect viability\(^{[35]}\). The excellent definition of endocardial and epicardial borders allows wall thickness to be measured accurately. Changes in wall thickening during the cardiac cycle in response to low doses of dobutamine can be used to assess viability. The various methods are all effective and to some extent complementary in assessing viability, with local expertise and facilities often determining the chosen method\(^{[36]}\).

The demonstration of viability is less important clinically than the prediction of recovery in function after revascularization. All of the above techniques have been shown to be reasonably successful at predicting post revascularization recovery of function in myocardial segments\(^{[37–39]}\). Despite the differences between the methods, the sensitivity and specificity for recovery of individual segments ranges between 70 and 90% for all the techniques. The positive predictive value for segmental contractile recovery lies between 70-90% across a range of studies using the various methods\(^{[37–39]}\).

It is now entirely possible in an individual with coronary disease to establish the presence of viable myocardium and predict likely improvement in ventricular function after successful revascularization. The wider issue of how many individuals, presenting for the first time with heart failure attributed to coronary artery disease, have a reversible element to their myocardial dysfunction remains unknown\(^{[40]}\).

**Therapeutic options**

Despite improved treatments for heart failure in the last decade morbidity and mortality remain high. In the Framingham study 1 year survival was 79% for men and 86% for women with only 38% of men and 58% of women alive 5 years after the development of heart failure\(^{[41]}\). Recent work from Hillingdon, West London reports a 1 year survival of 64% amongst a cohort of 220 cases of heart failure\(^{[41]}\). This compares with a 50-60% overall 5 year survival for colorectal cancer\(^{[42]}\). The variation in prognosis according to aetiology differs between studies. The community based Framingham study suggests a worse prognosis for non-ischaemic heart failure\(^{[43]}\). Hospital based prospective studies, which may be more selective, suggest a worse prognosis for those with ischaemic heart failure\(^{[44,45]}\). The difference may be due to many factors including the difficulty of establishing coronary heart disease as the causal mechanism for heart failure. Hospital based studies may have greater access to angiographic data revealing the presence of coronary artery disease in cases where this would not be detected in non-invasive community studies. There is also evidence suggesting that the presence of viable myocardium predicts a still worse prognosis\(^{[46]}\).

If this prognosis is to be improved, then we must utilize our current understanding of the different mechanisms of ischaemic heart failure to direct
treatment strategies. Treatments focusing on the idea that heart failure due to coronary heart disease may be a dynamic and partially reversible process, can be applied in different ways. Targets include preventing development of heart failure in those with coronary heart disease but without heart failure, strategies to prevent progression of transient heart failure (at times of acute ischaemia or myocardial infarction) into persistent heart failure, and treatments to prevent progression of chronic heart failure.

Recent successful secondary prevention trials in coronary heart disease have focused primarily on acute ischaemic end-points including myocardial infarction and sudden cardiac death[47]. This is in part due to the design strategy of the studies but perhaps also because less frequent heart failure end-points would require much larger studies for adequate power. However, analysis of the Scandinavian Simvastatin Survival Study Group trial data suggests heart failure was diagnosed less often in the simvastatin group compared with the placebo group[48]. These patients had coronary artery disease, but not heart failure at trial entry. It would seem plausible to extend this principle, of secondary prevention measures proven to reduce ischaemic end-points preventing the onset of heart failure, to other risk factors. Furthermore, it would seem appropriate for those already with ischaemic heart failure to address coronary heart disease risk factors as part of treatment to prevent progression of disease. Further myocardial infarcts are likely to worsen ventricular function. For patients with heart failure due to coronary artery disease, cholesterol reduction should be a priority and, although trial data is lacking, it would seem reasonable to add smoking cessation, hypertension control and aspirin therapy.

Several classes of drugs offer established or potential benefits for ischaemic heart failure. Angiotensin converting enzyme (ACE) inhibitors, with their proven benefit in systolic dysfunction and in patients post MI, are a mainstay of ischaemic heart failure therapy. The SOLVD prevention study showed a significant 37% reduction in the development of heart failure by an ACE inhibitor (enalapril)[49]. The treatment arm of the SOLVD study showed a 16% mortality reduction, with about 70% of cases having an ischaemic aetiology to their ventricular disease[50]. The AIRE (Acute Infarction Ramipril Efficacy) study showed a 27% reduction in 30 day mortality for patients with transient or persistent clinical evidence of heart failure, in the setting of acute myocardial infarction, taking ramipril compared to placebo[51]. ACE inhibitors are effective both in preventing clinical heart failure in those with asymptomatic ventricular dysfunction and in reducing mortality in those with overt heart failure. Their beneficial effects on haemodynamics as well as post-infarction remodelling make ACE inhibitors effective agents in patients with or without viable myocardium.

Beta-blockers have theoretically a number of useful actions in ischaemic heart failure. Anti-ischaemic effects and re-infarction reduction may slow development and progression of ischaemic heart failure. Beneficial haemodynamic effects, including reduction in afterload (particularly vasodilating beta-blockers) and wall stress, could also slow progression of ventricular dysfunction. The vasodilating beta-blocker, carvedilol has now been shown to improve mortality in selected patients with heart failure. Packer et al. showed a 38% reduction in hospitalization or death with carvedilol in patients with chronic heart failure of mixed aetologies[52]. Other trials of beta-blockers in heart failure have failed to show mortality benefits but a trial using metoprolol showed clinical benefits including reduced hospitalization[53]. The CIBIS study[54] (Cardiac Insufficiency Bisoprolol Study) showed benefits in clinical variables but any mortality benefits were limited to patients without previous myocardial infarction. Prevention of heart failure by the use of beta blockers has not been convincingly demonstrated in trials of patients with coronary heart disease, partly for similar reasons to statin therapy. The use of beta-blockers in heart failure is the subject of intense study and is being evaluated in a number of ongoing trials. However, the current data hints at potential benefits of beta-blockade.

Calcium channel blockers may also offer therapeutic benefits in ischaemic heart failure. Calcium ions have a central role in the mechanisms of stunning and hibernation. Calcium antagonists reduce ischaemia and may advantageously alter the raised cytosolic calcium levels proposed as part of the mechanism for stunning. Other effects of calcium antagonists, including negative inotropism, may be less advantageous. Clinical trials of calcium antagonists in heart failure have so far been disappointing. The PRAISE (Prospective Randomized Amlodipine Survival Evaluation) study, a recent trial using amlodipine in heart failure failed to show overall benefit of this calcium antagonist[55]. Subgroup analysis of the PRAISE study suggested any potential benefits were restricted to non-ischaemic heart failure patients. Smaller studies of other calcium antagonists including nisoldipine have, in contrast, been more encouraging[56], leaving the debate on the value of calcium antagonists in ischaemic heart failure unresolved.

It has long been known that left ventricular function can improve after revascularization[57,58]. Furthermore in patients with stable angina undergoing revascularization the relative mortality reduction is greatest in those with left ventricular dysfunction. The Coronary Artery Surgery Study (CASS) study, comparing bypass surgery with medical therapy, showed a 10 year survival in patients with ejection fractions less than 50% of 79% in the surgically treated group compared with just 61% in the medically treated group[59]. One larger comparative study of 701 patients with ischaemic heart disease and left ventricular dysfunction reported an 86% 3 year survival in the surgical group against 63% in those medically treated[60]. Less clear is to what extent revascularization prevents the development of heart failure. The recently published RITA-2 study comparing angioplasty with medical therapy in 1018 patients showed a non-significant reduction in new onset...
heart failure in the angioplasty treated group, a secondary event in the trial.[61] As with many trials in coronary heart disease the very small numbers (8 vs 15) of heart failure end-points make interpretation difficult. Development and progression of heart failure has not been a primary end-point in these studies. More importantly the earlier studies comparing bypass surgery with medical therapy did not separate impaired ventricles with viable myocardium, whose function might improve with revascularization, from those with predominantly scarred ventricles.[59] Potential improvements of left ventricular function in some subgroups would have been diluted by other cases. This is supported by evidence that identifying patients using viability studies and then selectively revascularizing improves morbidity and mortality compared to matched controls.[62] Selective revascularization based on hibernation studies has been successfully employed across the spectrum of ischaemic heart failure including patients planned for transplantation[63] and those with or without angina.[64,65]. At present the patients in these studies represent selective small series. Encouraging data from these studies suggests the need for clinical trials randomising unselected patients to viability directed revascularization or standard therapy.

Conclusions

Ischaemic heart disease is the leading cause of heart failure in our society. Ischaemic cardiac dysfunction is a complex interplay of mechanisms and is potentially a reversible process underpinned by the existence of viable myocardium. Reversal of left ventricular dysfunction, with improvement in mortality and morbidity, may well be achieved by revascularization and potentially by appropriate medical therapy. There remain many unanswered questions. How much incident heart failure is due to ischaemic disease and what proportion of these patients have a substantially reversible element to their contractile deficit has not been established. Similarly, whether tailored therapy based on thorough investigation with angiography and viability studies followed by medical and revascularization strategies is more effective than current therapies is unknown. These issues can only be truly tested in a randomized study.

In managing patients with ischaemic heart failure, seeking and treating viable myocardium is a realistic option. Until trial data is available, the benefits can only be guessed, but the barriers to improving the outlook for ischaemic heart failure may be breaking down with the advent of a new understanding of the condition and more effective treatment strategies.

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References


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