Treatment paradigms in heart failure

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Heart failure patients suffer very severe morbidity, high mortality and are common in medical practice. Their need for effective treatments is only partially answered by current options. Effective treatments often address cellular and pathophysiological mechanisms which are involved in the progression of heart failure. This article reviews those mechanisms and treatments.

A frequently quoted definition of heart failure describes it as 'the pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirements of the metabolising tissues, or can do so only from an elevated filling pressure' (Braunwald, 1994). A more clinically useful definition proposed by the European Society of Cardiology is 'the symptoms of heart failure, objective evidence of cardiac dysfunction and response to treatment directed towards heart failure' (Task Force on Heart Failure of the European Society of Cardiology, 1995).

These descriptions gloss over the multiplicity of underlying aetiologies and the vast range of adaptive and maladaptive mechanisms which come into play when the heart fails. Examples include neuroendocrine activation with raised levels of noradrenaline (Francis et al, 1993), renin–angiotensin–aldosterone (RAA) activation (Swedberg et al, 1990), increases in atrial natriuretic peptide and brain natriuretic peptide (Benedict et al, 1993), tumour necrosis factor-α and endothelins. Additional problems are myocardial hypertrophy, interstitial fibrosis and loss or blunting of functional mechanisms, such as the Frank–Starling mechanism and force–frequency responses, poor myocardial relaxation and incoordinate contraction secondary to conduction abnormalities. Left ventricular performance may be further compromised by functional mitral regurgitation secondary to annular dilatation.

Many of these mechanisms associated with heart failure may be detected long before there are overt signs of myocardial dysfunction, and neuroendocrine disturbances in particular have been shown to have prognostic importance. New treatments need to address these pathophysiological mechanisms.

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THE MEDICAL OPTIONS

Angiotensin-converting enzyme inhibitors and other RAA system antagonists

The mainstay of heart failure treatment continues to be diuretics and vasodilators and these require little introduction. Angiotensin-converting enzyme (ACE) inhibitors have become the first choice of vasodilator since the explosion of data on mortality starting in the 1980s with trials such as CONSENSUS (CONSENSUS Trial Study Group, 1987), SAVE (Vantrimpont et al, 1997), SOLVD (SOLVD Investigators, 1991), TRACE (Kober et al, 1995) and AIRE (Acute Infarction Ramipril Efficacy (AIRE) Study Investigators, 1993). An alternative vasodilator, hydralazine, also demonstrated a reduction in mortality compared with placebo in the Veterans Administration Heart Failure Treatment (VeHeFT) trial (Cohn et al, 1986). Attention has focused on how ACE inhibitors might exert their beneficial effects over and above vasodilatation. Proposed mechanisms include influencing ventricular remodelling by helping to maintain an ellipsoid rather than spherical shape, effects on myocardial fibrosis, arrhythmias and, most importantly, blockade of the RAA system, which undergoes increased activation in heart failure.

The neuroendocrine hypothesis of heart failure progression proposes that activation of the RAA system initially represents a reactive compensatory mechanism in response to tissue hypoperfusion (specifically of the juxtaglomerular apparatus of the kidney). However, the resulting sodium and water retention is thought to cause a deleterious chronic additional load on myocardial function which advances rather than halts the disease process. Data showing that the degree of activation of the RAA system is an independent predictor of adverse outcome in heart failure (Francis et al, 1993) support this hypothesis. The credibility of the neuroendocrine hypothesis is enhanced by data

from randomized trials showing that drugs that antagonize the RAA system reduce mortality and improve symptoms in patients with heart failure. These drugs are ACE inhibitors, angiotensin II antagonists (losartan and valsartan) and the recently rehabilitated aldosterone antagonists (spironolactone) (RALES Study Group, 1996).

In the Valsartan in Heart Failure (Val-HeFT) trial (Cohn and Tognoni, 2001), the angiotensin II inhibitor valsartan was randomized against placebo in heart failure patients who were already on ACE inhibitors and optimal current treatment. All-cause mortality was not affected, although hospitalization for heart failure was reduced by 27%. Initial hopes from ELITE I (a dose-ranging trial) that the angiotensin II receptor antagonist losartan would prove more effective at reducing mortality than captopril were not confirmed by the follow-up ELITE II trial, which found the two drugs to be equivalent in efficacy (Pitt et al, 1997, 2000).

The aldosterone antagonist spironolactone, which had previously fallen out of favour with cardiologists for being an ineffectual diuretic with a tendency to increase potassium and provoke unwanted side effects, such as gynaecomastia, has had something of a renaissance since the RALES trial was published (Pitt et al, 1999). This study looked at 1663 patients on optimal heart failure treatment including ACE inhibitors. It showed a 30% reduction in mortality with spironolactone in comparison with placebo and a 30% reduction in hospitalization. There was a significant improvement in heart failure symptoms, as assessed by the New York Heart Association (NYHA) functional class, and there was little clinically significant increase in serum potassium levels (serious hyperkalaemia 2% *vs* 1% placebo, *P*=not significant).

Beta blockade and the sympathetic nervous system

The concept that the compensatory overactivity of neuroendocrine pathways is central to deteriorating heart failure has been applied to the possible damaging effects of chronic noradrenaline from an overworked sympathetic nervous system. Raised noradrenaline levels correlate with poor prognosis and severity of heart failure. Adrenergic overactivity was first recognized nearly 40 years ago (Gaffney and Braunwald, 1963) and for a long time was regarded as simply a compensatory mechanism for maintaining cardiac output in the face of declining myocardial efficiency. There has been a growing awareness that this sympathetic activation (like RAA activation) might have a part to play in the progression of declining myocardial function (Packer, 1990).

One of the disappointments of cardiovascular therapeutics has been the failure of inotropic interventions in heart failure. Many have been tried, in particular beta agonists such as dobutamine (Elis et al, 1998), phosphodiesterase inhibitors (Packer et al, 1991) and partial beta-receptor agonists such as xamoterol (Xamoterol in Severe Heart Failure Study Group, 1990), but all have had a deleterious effect on mortality in clinical trials. These inotropic drugs all act by increasing intracellular cyclic adenosine monophosphate (cAMP) and hence intracellular calcium cycling via the beta receptor signal transduction pathway.

The one inotropic agent which does not appear to have an adverse effect on mortality is digoxin (Digitalis Investigation Group (DIG), 1997), and its primary mode of action results in increased intracellular sodium rather than cAMP. Moreover, its chronic administration is associated with a reduction in noradrenaline levels (Krum et al, 1995). In the DIG trial, which investigated the effectiveness of digoxin in patients in sinus rhythm and heart failure, it was found to be no more effective in preventing death than placebo although there was some evidence for reduced hospitalization. However, the digoxin withdrawal trial found that once established on the drug, it was more harmful withdrawing digoxin therapy than continuing with it (Uretsky et al, 1993).

While drugs which increase intracellular cAMP appear to increase mortality, beta blockers, which antagonize cAMP production, seem to reduce mortality and improve symptoms in heart failure. Arrhythmia prevention may provide part of the explanation, but it neither explains the extent of the reduction in mortality, nor the ability of beta blockers to reduce hospitalization and improve heart failure symptoms over the medium term.

Human myocytes from non-failing hearts have both β_1- and β_2-receptors in a ratio of approximately 2:1. In a failing human myocardium, the number of β-receptor is reduced, primarily as a result of decreased β_1-receptors resulting in an increased reliance on the β_2-receptor subtype (Bristow et al, 1982). Both receptor subtypes are coupled through G proteins to adenylyl cyclase and increase intracellular cAMP when stimulated. This in turn results in an increase in the activity of protein kinase A, which, by phosphorylating key proteins such as phospholamban and L-type calcium channels, causes an increase in cellular calcium loading and the magnitude of systolic calcium release by the sarcoplasmic reticulum (SR) (*Figures 1* and *2*). The result is a large increase in the force of myocyte contraction and in the rates of contraction and relaxation. This system

of inotropic control is both potent and extremely sensitive with 5–10 times increases in contractile force over baseline with nanomolar concentrations of beta agonists, such as isoprenaline, in isolated cell experiments from normal hearts.

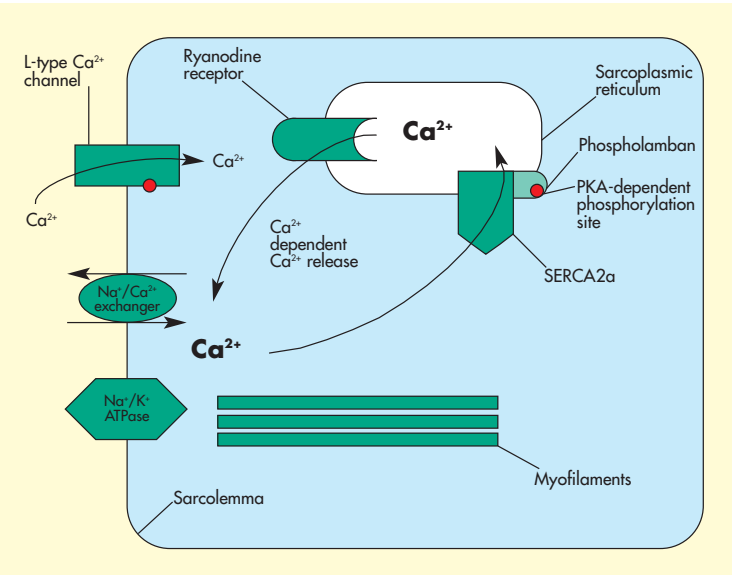
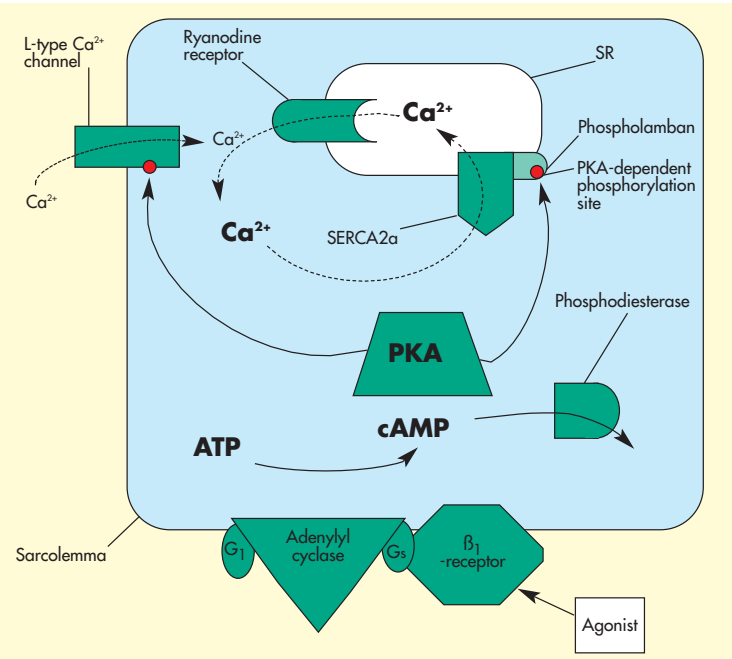


Figure 1. Cardiac myocyte calcium cycling. Calcium cycles between the myofilaments in the cytosol and the sarcoplasmic reticulum (SR) where it is stored. It is released from the SR during systole via the ryanodine receptor in response to calcium coming into the cell through L-type channels. It is taken back into the SR by the SR calcium ATPase (SERCA2a) during diastolic relaxation of the cell. Sites phosphorylated by protein kinase A (PKA) (red circles) result in more calcium entering the cell and faster uptake into the SR. This causes increased cellular calcium loading with resultant increases in contractile force and rates of relaxation. In heart failure, these processes are blunted with diminished contractile force and poor diastolic calcium reuptake by the SR, i.e. loss of inotropic response and reduced diastolic compliance.



No other cellular pathway has such a marked effect on cellular contraction, and this suggests that the β-receptor signalling pathway is the main physiological 'accelerator' for myocardial function. In heart failure, this pathway is markedly blunted – β-receptor number is reduced and the effect of beta agonists are partially uncoupled by inhibitory G proteins and receptor phosphorylation from cAMP production. Consequently, cAMP levels are found to be low and contractile responses to agonists are reduced. In addition, there appears to be a reduction in proteins, such as the SR calcium ATPase (SERCA2a), which actively pumps calcium back into the SR. Reduction in SERCA2a activity results in impoverished calcium cycling by cardiomyocytes. In heart failure, there is therefore more than simply loss of myocytes – those that remain offer poor contractile responses in the face of an ever-increasing sympathetic drive.

Some investigators believe that the chronic increase in noradrenaline levels, in response to sympathetic activation in heart failure, causes the blunting of β-receptor response. This effect may be partially reversed by the use of beta blockers, which competitively antagonize the negative, downregulating effects of chronic sympathetic activation on cellular signal transduction.

Although beta blockers have traditionally been contraindicated in heart failure because of their negative inotropic effects, the evidence that they might reduce mortality when chronically used in heart failure has been clear for many years but largely unnoticed within various post-myocardial infarction trials.

This led to the seemingly paradoxical idea that beta blockers, if used with care, might prove a useful treatment for chronic heart failure. Yet, patients treated with metoprolol have been found to have better exercise tolerance and a reduction in baseline noradrenaline levels (Andersson et al, 1991). That this translates into a reduction in mortality has now been confirmed in a series of

Figure 2. Beta receptor/cyclic adenosine monophosphate (cAMP) signal transduction pathways. Binding of agonist to β-receptors results in increased cAMP production mediated by adenylyl cyclase and G proteins. cAMP activates protein kinase A (PKA). PKA phosphorylates a variety of targets, such as L-type Ca^{2+} channels, which increases intracellular Ca^{2+} and thus systolic contraction. Reuptake of Ca^{2+} into the sarcoplasmic reticulum (SR) is performed by the SR calcium ATPase (SERCA2a), which is regulated by phosphorylation of phospholamban which is also PKA dependent. This results in a faster clearance of calcium from the cytosol (the key process in diastolic relaxation of the heart). In heart failure, β-receptors are desensitized and reduced in number, resulting in low levels of cAMP and reduced Ca^{2+} cycling.

placebo-controlled studies in which beta blockers have been given to patients with varying degrees of heart failure, starting at very low doses which are progressively increased over a period of weeks and months (MDC, ANZ, US-HF, CIBIS I and II, MERIT-HF and COPERNICUS – for details, see *Table 1*). These studies have looked variously at metoprolol, bisoprolol and carvedilol – the latter supposedly having the advantage in heart failure of a vasodilator action through α-receptor antagonism, potentially allowing greater tolerability. While this may prove a helpful marketing strategy for carvedilol over its competitors, the mortality data and reduction in heart failure progression are impressive for every beta blocker so far tested (*Table 1*), except bucindolol, which did not show a significant reduction in mortality in the BEST trial, although there were fewer hospitalizations (Domanski, 1999).

Meta-analysis has suggested that beta blockers, while significantly reducing all-cause mortality in patients with both ischaemic and dilated cardiomyopathies, have a more marked impact in reducing non-sudden cardiac death compared with sudden cardiac death. This implies that the effects of beta blockade are more important in reducing heart failure progression than in preventing sudden arrhythmic death. However, data from CIBIS II have suggested that bisoprolol is effective in reducing both categories of death.

Amiodarone

The apparent antiarrhythmic effect of beta blockers has not yet lead to success with other classes of antiarrhythmics in heart failure, of which amiodarone held the most promise. No individual study has shown a reduction in mortality in heart failure with amiodarone. Some investigators have pointed out a lack of power in these studies to detect such a reduction. A meta-analysis of the amiodarone data has suggested a small reduction in all-cause mortality of 13%, increasing to 29% when only sudden, and therefore presumed arrhythmic, deaths are included (Amiodarone Trials Meta-Analysis Investigators, 1997). However, the use of amiodarone in heart failure patients without evidence of important arrhythmias remains controversial.

Endothelin antagonists

Other neuroendocrine factors may be therapeutic targets in heart failure treatment. Interest has focused on endothelin antagonists such as tezosentan since endothelins are elevated in heart failure. One recent study comparing tezosentan with placebo in patients in NYHA class III and IV demonstrated a dose-dependent increase in cardiac index ranging from 24–50% compared with placebo. This was in addition to reductions in peripheral and pulmonary vascular resistance and pulmonary wedge pressure (Torre-Amione et al, 2001). Whether these haemodynamic changes will culminate in reductions in mortality and morbidity has yet to be determined. A phase III study of tezosentan in 292 patients (RITZ-2) showed promising results and was presented as a late breaking trial at the American College of Cardiology conference in March 2001.

THE PROBLEM OF DIASTOLE

There has been much interest recently in 'diastolic heart failure'. This has developed from the realization that up to 30% of patients fulfiling the Framingham criteria for heart failure do not appear to have any significant systolic abnormality (McKee et al, 1971). This has lead to the

TABLE 1.
The beta blocker in heart failure trials

Trial and reference	n	Aetiology	Beta blocker	% reduction in all-cause mortality	Comments
MDC, Waagstein et al (1993)	383	DCM	Metoprolol	34	Improved exercise time
CIBIS I, CIBIS Investigators and Committees (1994)	641	IHD, DCM	Bisoprolol	20 (ns)	Reduced hospitalization
US-HF, Packer et al (1996)	1094	IHD DCM	Carvedilol	65	Quality of life and EF improved at 6 months and reduced hospitalization
ANZ, Australia/New Zealand Heart Failure Research Collaborative Group (1997)	415	IHD	Carvedilol	ns	Improved EF at 6 months and reduced hospitalization
CIBIS II, CIBIS-II Investigators (1999)	2647	IHD, DCM	Bisoprolol	32	
MERIT-HF, MERIT-HF Study Group (1999)	3991	IHD, DCM	Metoprolol	49	
COPERNICUS, Carvedilol Prospective Randomised Cumulative Survival Trial Investigators (2001)	2289	severe HF	Carvedilol	35	24% all-cause mortality and hospitalizations
BEST, Domanski (1999)	2708	Moderate to severe HF	Bucindolol	10 (ns)	Placebo better in African Americans

DCM = dilated cardiomyopathy; EF = ejection fraction; HF = heart failure; IHD = ischaemic heart disease; ns = non-significant. ANZ = Australian/New Zealand study; BEST = Beta Blocker Evaluation of Survival Study; CIBIS = Cardiac Insufficiency Bisoprolol Study; COPERNICUS = Carvedilol Prospective Randomised Cumulative Survival Trial; MDC = Metoprolol in Dilated Cardiomyopathy; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial; US-HF = United States Carvedilol Heart Failure

hypothesis that abnormalities of cardiac filling during diastole might result in a failure of cardiac reserve and symptoms of breathlessness and poor exercise tolerance. One might equally argue that the criteria for diagnosing heart failure are not very specific, and evidence suggests that a significant number of patients with 'diastolic heart failure' has had respiratory disease, atrial fibrillation or angina misdiagnosed (Caruana et al, 2000).

The diastolic heart failure hypothesis proposes that there is poor, delayed myocardial relaxation in this condition. This results in a stiff, non-compliant left ventricle which can only be filled properly with the aid of high diastolic filling pressures. In this scenario, normal systolic function will not help a heart which cannot fill properly.

One difficulty with this theory is that diastolic dysfunction is not readily detected or easily measured non-invasively. Echocardiography cannot measure myocardial compliance, although this has not prevented investigators using the technique as the gold standard in making the diagnosis. Echocardiographers look for evidence of a 'restrictive filling pattern' using the ratio of early diastolic to atrial transmitral blood flow velocities (E:A ratio), deceleration times, tissue Doppler and the rate of propagation of blood velocity within the left ventricle. However, these parameters, being related to velocities rather than compliance, are indirect and dependent on variables such as filling pressures, afterload and age. In truth, there is no non-invasive method of determining the pressure required to fill a ventricle with a particular volume of blood. There is, therefore, debate as to the sensitivity and specificity of echo for diastolic heart failure. However, data are available to suggest that patients with 'restrictive filling' on echocardiography have a worse prognosis than those with normal diastolic function.

Despite the diagnostic difficulties, there are good pathophysiological reasons why diastolic dysfunction might exist. Muscle strips and myocytes from patients with systolic heart failure have been shown to relax more slowly than normal tissue. Myocardial relaxation is not simply a passive process resulting from the 'springing back' of elastic tissues – it is an active process requiring the hydrolysis of adenosine triphosphate (ATP) to remove cytosolic calcium from the contractile myofilaments. This is done predominantly by SERCA2a, together with the sarcolemmal Na/Ca exchanger. Patients with heart failure have functionally impaired SERCA2a (there is an ongoing controversy in the literature as to whether this is the result of reduced SERCA2a protein levels or increased inhibition of SERCA2a by its regulatory protein phospholamban). There is some evidence that this deficit is partially compensated by an upregulation of Na/Ca exchanger activity.

Most importantly, these are patients with systolic heart failure that have been shown to have abnormalities of relaxation. Impoverished contraction and lacklustre filling can be viewed as two sides of the same coin. In this model, poor diastolic uptake of calcium into the SR on one beat results in poor calcium release from the SR on the next beat. While we worry about the existence of a separate entity called diastolic heart failure, it is possible that the majority of patients with heart failure may have impaired diastolic function, and finding ways to modify this is thus an important therapeutic challenge.

Basic scientists have already started to use genetic techniques to investigate the function of these proteins, using transgenic mice in which candidate proteins, such as phospholamban and SERCA2a, are either overexpressed or knocked out. Methods are already available for increasing SERCA2a expression in vivo using adenovirus as a vector for genetic material. While these techniques have not been used in vivo in man, the feasibility of inserting SERCA2a DNA with a resultant upregulation of that protein has been demonstrated in vitro in human myocytes.

While this sounds somewhat closer to science fiction than fact, as discussed previously, other treatments, such as beta blockers, may derive their therapeutic effects through modifying these cellular pathways.

MECHANICAL APPROACHES

Transplantation and bridges

Transplantation is hampered by low organ availability (for example, only approximately 300 transplants are performed a year in the UK with a waiting list of some 3000). It continues to have an important role in younger patients with severe heart failure without serious comorbidity. However, the number of organs available in most countries is far fewer than is needed to make a significant impact.

Efforts are being made to ease this shortage of donor organs by breeding transgenic animals, such as pigs, which do not express some of the cell surface antigens leading to rejection but which possibly express human HLA markers in the future. This approach has been caught in the crossfire between ethical considerations, animal rights concerns and anxieties about the potential cross-species spread of animal viruses.

With such an excess of patients on waiting lists for transplantation, interest has focused on finding a 'bridge' to transplantation. Work on artificial hearts or left ventricular assist devices has

begun to provide new solutions to problems such as infection, maintaining a power supply, thromboembolic phenomena and red cell trauma. One device uses a 'push/pull' plate to pump blood, and the latest and smallest device so far, called the Jarvik 2000, has an impeller mechanism (Archimedes screw) which is used to drive blood from the left ventricle to the descending aorta. It is designed to offload the left ventricle and supplement cardiac output. Some patients need two pumps for biventricular failure – one for the right and the other for the left heart (BiVAD). An anecdote from Papworth tells of one patient with a BiVAD who surprised staff by nonchalantly continuing his breakfast while his heart went into ventricular fibrillation (VF).

Some patients with these devices appear to have a significant and sustained improvement in myocardial function. Some no longer need to be on the transplant list. A few have even had the device successfully removed – the so-called 'bridge to recovery'.

Surgical fixes

The Batista operation was designed to remodel the left ventricle and improve mitral valve function by removing a wedge of the left ventricle, thus reducing cavity size (Batista et al, 1996). By fashioning a smaller ventricle, the aim was to decrease wall stress according to Laplace's law, which defines the relationship between wall stress, wall thickness and cavity diameter – dilated thin-walled chambers having the greatest wall stress. From its inception, the operation has been controversial, not least because of the necessity of dissecting away viable tissue in exchange for an 'optimal' ventricular shape. While Batista himself appeared to have significant success with the operation, predominantly in patients with a dilated cardiomyopathy secondary to Chaga's disease, other groups have had mixed results (Gorcsan et al, 1998).

Less radical approaches, such as aneurysmectomy, achieve the aim of the Batista operation by improving ventricular geometry without removing viable muscle. Alternatively, mitral valve function, which is frequently regurgitant in the presence of a dilated left ventricle and atrioventricular ring, can be addressed. Either surgical repair or insertion of an annuloplasty ring can improve the continence of the valve and thus the efficiency of left ventricular function. Results so far are promising but clearly depend on careful case selection of patients with important functional regurgitation (Chen et al, 1998).

The development of nuclear and positron emission tomography scanning techniques for identifying tissue viability, particularly in patients with heart failure resulting from ischaemic heart disease, has lead to increasing recognition of hibernating myocardium – myocardial muscle which is alive but poorly contracting in areas of low tissue perfusion. Surgical revascularization may be beneficial in selected cases, and there is observational support for this strategy from the Collaborative Study in Coronary Artery Surgery (CASS) registry (Alderman et al, 1983). These surgical techniques – coronary artery bypass grafting, mitral valve repair and aneurysmectomy – can be combined in appropriate cases, but the operative morbidity and mortality of operating in patients with severe heart failure will remain a disincentive to the widespread use of surgery despite some encouraging data. Other, even more elaborate techniques, such as cardiomyoplasty, where the heart is wrapped up in the transplanted latissimus dorsi muscle, are unlikely to become popular, as the procedure is complex, prone to complication and probably unsuccessful, although it still retains a few adherents (Cruz et al, 1997).

Electrophysiological strategies

A common occurrence in heart failure is the development of conduction abnormalities with widening of the QRS complex. This is thought to reflect incoordinate contraction, and therefore relaxation, of the left ventricle. Several studies have shown that prolonged activation in heart failure is an independent predictor of mortality (Shamim et al, 1999). Functional mitral regurgitation continues after closure of the aortic valve during the period of 'isovolumic' relaxation (clearly not isovolumic if the ventricle is continuing to empty into the left atrium). This mitral regurgitation can be exacerbated by incoordinate relaxation and may persist well into diastole, thereby compromising ventricular filling.

Similarly, a long PR interval may not be desirable – the optimum moment for the onset of ejection is as soon as filling is complete, and any delay may result in presystolic mitral regurgitation. These observations have lead to an interest in the possibility that dual and biventricular pacing might be used to optimize cardiac performance, and this approach is under investigation. Biventricular pacing involves placing conventional leads in the right atrial appendage and ventricle, with a third lead in the coronary sinus stimulating the left ventricle. This allows the right and left ventricles to be depolarized simultaneously, resulting in a better coordinated ventricular contraction. This is technically challenging to do, and it seems likely that any potential benefits will need to be clearly demon-

strated before this will become a widespread treatment. Early data from the Multi-site Stimulation in Cardiomyopathy Trial (MUSTIC) and the InSync Trial have been encouraging (Abraham, 2000; Cazeau et al, 2001).

Another electrophysiological approach to treating heart failure is the increasing use of implantable cardiac defibrillators (ICDs) in patients with documented life-threatening ventricular arrhythmias. ICDs are similar to oversized pacemakers, with a large lead positioned in the right ventricle which can deliver a DC shock capable of cardioverting the patient from a life-threatening arrhythmia, such as ventricular tachycardia (VT) or VF. The device is able to distinguish different types of arrhythmia and may have additional pacing functions, including overdrive pacing for VT.

Several recent trials have demonstrated the efficacy of ICDs in reducing sudden death from arrhythmias. The two most important are MADIT (Multicenter Automatic Defibrillator Implantation Trial) and the AVID (Antiarrhythmics Versus Implantable Defibrillators) trial (Multicenter Automatic Defibrillator Implantation Trial Investigators, 1996; AVID Trial Investigators, 1999). MADIT specifically looked at patients (n=196) with left ventricular dysfunction (ejection fraction < 35%) who had had previous myocardial infarction, a previous non-sustained VT and inducible VT during electrophysiological testing. Over a 27-month follow-up, there were 15/95 deaths in the ICD group compared with 39/101 (P=0.009) in the conventional therapy group (predominantly treated with amiodarone or beta blockers). AVID enrolled 1016 patients who had survived VF or sustained VT were randomized to ICD or antiarrhythmic therapy. Of 202 deaths, 122 were taking antiarrhythmics and 80 had ICDs (P=0.012). When the mode of death was considered, ICDs were found to significantly reduce arrhythmic deaths and had no effect on non-arrhythmic cardiac deaths and non-cardiac deaths.

KEY POINTS

- Heart failure is a complex multisystem disorder involving deleterious changes in several neuroendocrine systems as well as failures in myocardial contraction and relaxation.
- Medical treatments that reduce mortality have largely had effects on neuroendocrine systems, such as angiotensin-converting enzyme inhibitors, angiotensin inhibitors, spironolactone and beta blockers.
- Inotropes, working predominantly through cyclic adenosine monophosphate augmentation, have largely had harmful effects. The exception is digoxin (with a different mode of action), which does not appear to increase mortality unless it is withdrawn.
- Antiarrhythmics have been disappointing with the possible exception of amiodarone. The most effective antiarrhythmic is an implantable cardiac defibrillator, but only in selected cases.
- Surgeons have an important role in selected cases where revascularization, valve repair, aneurysmectomy, ventricular assist devices or transplantation is contemplated.
- Diastolic dysfunction (failure of cardiac relaxation) may well be important, but knowledge and treatment strategies are currently limited.
- Heart failure affects 2% of the population and 10% of the elderly.

EXERCISE

Physical exercise and formal exercise training have become increasingly popular as a treatment for heart failure. Investigators have shown that suitable programmes can result in increases in stamina and improvements in respiratory function and perceived quality of life. This appears to be achievable without any increase in risk to the patients (Coats et al, 1992). One hypothesis is that exercise training helps correct skeletal muscle functional and metabolic abnormalities. Most studies investigating this have looked at training over 1–3 months. Longer term outcomes are less certain, and no studies have been powered to assess mortality.

CONCLUSIONS

Heart failure will continue to be a major health problem in the future. Treatments increasingly focus on the underlying pathophysiological mechanisms, especially neuroendocrine mechanisms such as the RAA system, endothelins and the sympathetic nervous system, cellular and genetic mechanisms, and mechanical or surgical approaches which can support the circulation. This is all in addition to the humble diuretic treatments. Despite this, heart failure is associated with huge morbidity and mortality, which continues to rise with increases in life expectancy and the rise in the number of heart attack survivors. HM

Conflict of interest: none.

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