Current and future options for the management of heart failure

In this science article, John Sherwood, Mark Ashton, Claire Newton and Sumita Biles examine the pathophysiology of heart failure, current treatments available, and research and development into new treatments.

Chronic heart failure is an increasing problem worldwide. There are around 900,000 people with heart failure in the UK and almost as many with damaged hearts but without any symptoms of heart failure. Heart failure is a complex syndrome of symptoms and signs. If left untreated, it has a poor prognosis, but mortality and morbidity can be greatly improved by early, targeted treatment.

The most common causes of chronic heart failure in the UK are coronary heart disease and hypertension, with many patients having had a myocardial infarction in the past. Associated risk factors, such as an ageing population, increases in the rates of diabetes mellitus and hyperlipidaemia, and smoking, have also contributed to the increasing prevalence of heart failure in the UK.

Pathophysiology

The heart acts as a pump to support physiological circulation. Any disruption to the normal functioning of the heart can lead to heart failure and decreased cardiac output. This, in turn, decreases the perfusion of metabolising tissues and reduces the function of many organ systems. The most common symptoms of heart failure are breathlessness, fatigue at rest or on minimal exertion and fluid retention (eg, ankle swelling). Diagnosis of heart failure is based on history, examination and investigations, such as echocardiography.

Patients with heart failure are almost equally divided into those with left ventricular systolic dysfunction (LVSD) and those with heart failure but with preserved ejection fraction. Ejection fraction is the fraction of blood ejected by the left ventricle during the contraction phase of the cardiac cycle (systole). Although the general approach to care is the same whether systolic function is reduced or not, most of the current evidence on drug treatment is for heart failure due to LVSD. The heart works on two main compensatory mechanisms to maintain adequate tissue perfusion. These are the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAS). Activation of the SNS causes vasoconstriction. This, in turn, raises blood pressure, heart rate and cardiac afterload. The SNS also causes an increase in renal vascular resistance thereby reducing renal perfusion and increasing renin secretion.

Renin is an enzyme that stimulates the production of angiotensin I and, in turn, angiotensin II. Angiotensin II can also stimulate the adrenal cortex to produce aldosterone. Activation of the RAS can increase sodium and water retention in the body, causing oedema and a rise in blood pressure.

Current treatments

Treatment of heart failure is based on targeting both the SNS and the RAS. The National Institute for Health and Clinical Excellence (NICE) has recently produced updated guidelines on the treatment of heart failure. Essentially, for those with preserved ejection fraction, it is imperative to control co-morbidities such as hypertension, ischaemic heart disease and diabetes and to provide lifestyle advice (eg, smoking cessation).

A loop diuretic should be used as needed for symptom control of congestion and fluid retention. For those with LVSD, there is a stepwise approach to treatment depending on response and function. First-line pharmacological treatments include angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for those who cannot tolerate an ACE inhibitor. These both work to inhibit the RAS. It is known that angiotensin II is an important factor in cardiac remodelling and left ventricular dysfunction. In addition, a beta-blocker licensed for the treatment of heart failure is also recommended. These drugs work by suppressing the SNS and RAS to provide cardio-protection.

If a patient remains symptomatic following treatment with both an ACE inhibitor and a beta-blocker, an aldosterone antagonist should be introduced. Aldosterone has an important role in the pathophysiology of heart failure. It causes sodium retention and potassium loss, and may contribute to sympathetic activation, parasympathetic inhibition, endothelial dysfunction and vascular fibrosis. These effects have provided the incentive to...

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investigate the potential benefit of drugs that lower plasma aldosterone levels or antagonise its effects. ACE inhibitors and ARBs cause a decrease in plasma aldosterone concentration, but this is only temporary. As treatment continues, the level of aldosterone returns to normal and, in some patients, may exceed the normal level. This phenomenon, known as "ACE escape", may offset some of the cardioprotective effects seen with ACE inhibitors or ARBs.4

Until recently, spironolactone was the only aldosterone antagonist licensed for heart failure. Spironolactone also blocks androgen receptors and is an agonist at progesterone receptors. This can lead to gynaecomastia, impotence and decreased libido. It can also cause hyperkalaemia, which is a particular risk if it is combined with ACE inhibitors. Spironolactone significantly reduces rates of mortality, decreases hospital admissions and improves symptoms in patients with heart failure who are already receiving standard heart failure therapy.

Eplerenone is a derivative of merenone, an aldosterone antagonist similar to spironolactone. The merenone molecule was modified with the aim of reducing the likelihood of the unwanted effects characteristic of spironolactone. Eplerenone is 100 times more specific for the aldosterone receptor than spironolactone. It is also much less potent at blocking androgen receptors than spironolactone and has no activity at progesterone receptors.1 However, like spironolactone, it can cause hyperkalaemia.

It is licensed for use in addition to standard therapy in stable patients with LVSD with clinical evidence of heart failure following a myocardial infarction. It should be started within 14 days of the myocardial infarction. There have been no direct comparisons between the two drugs and there is no evidence that it is more effective than spironolactone when used in patients with chronic heart failure.

However, a recent study5 found that adding eplerenone to recommended therapy for patients with mild heart failure did reduce death from cardiovascular causes and hospital admissions. Whether spironolactone would produce the same results at a much lower acquisition cost is unknown.

Current areas of research
Natriuretic peptides
An important component of cardiorenal homeostasis is provided by the natriuretic peptides (NP) atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP).

The levels of ANP and BNP are elevated in both long-standing heart failure and hypertension. The level of BNP is often measured to confirm a diagnosis of heart failure and it is known that eplerenone reduces the level of BNP in plasma. ANP is produced and released by cardiomyocytes, while BNP is produced and released by both cardiomyocytes and cells of the central nervous system.

CNP is a vasodilatory peptide produced in vascular endothelium cells. Both ANP and BNP exhibit a range of actions. The main effects include natriuresis, arterial vasodilatation, inhibition of RAS, inhibition of sympathetic nervous function, inhibition of endothelin, inhibition of vasopressin and adrenoconstrictorotropic hormone. All three peptides exert their respective effects by binding to cyclic guanosine monophosphate — natriuretic peptide receptors (NPR). NPR-A binds ANP and BNP; NPR-B binds CNP and NPR-C binds all natriuretic peptides.7

Due to the important role of NPs in cardiorenal homeostasis, there has been a lot of interest in using them to treat heart failure and a recombinant human BNP called nesiritide® is approved for the short-term treatment of congestive heart failure in the US. Originally licensed in 2001, a number of studies suggested that nesiritide was linked to a higher incidence of death than conventional treatments like diuretics and vasodilators, and a large phase III trial is under way to try to clarify the situation.

A new synthetic NP therapy is under development by Nile Therapeutics Inc. CD-NP® is a combination of two fragments of NPs and is currently undergoing phase II trial. The peptide is composed from dendroaspis NP (originally isolated from the venom of the green mamba snake, but also present in humans) and CNP. CD-NP binds to all NPRs and has a number of favourable characteristics, including antifibrotic effects, renoprotective properties (produced by the DNP component), and relaxation of veins.

Cinaciguat
Nitric oxide (NO) is produced in endothelial cells in response to a number of factors, including the shear stress caused by blood flow and a range of endogenous molecules, such as vasopressin, bradykinin, thrombin, catecholamines, oxytocin, endothelin-1 and histamine. Each of the endogenous molecules activates a specific receptor that is coupled to a G-protein, which, in turn, activates endothelial NO synthase, which produces NO.

The NO generated causes the inhibition of a number of processes, including the production of endothelin-1, the expression of adhesion molecules and the contraction of vascular smooth muscle. The effects of NO are mediated through its activation of the cysolic enzyme soluble guanylate cyclase (sGC). The activation of sGC by NO causes the conversion of guanosine triphosphate to cyclic guanosine-5’,5’-monophosphate (cGMP). cGMP is an important signalling molecule involved in the regulation of a number of cellular processes, which, ultimately, lead to vasodilatation. Due to the central role played by sGC, a number of companies are pursuing development programmes in this area.6 Bayer has a candidate in phase III trial called cinaciguat (BAY 58-2667), which is a potent activator of sGC. A particularly attractive feature of cinaciguat is its duration of action, which is longer than comparable medicines based on NO.

Conclusion
Heart failure represents a significant financial challenge for the NHS. With an ageing population and the fact that the disease tends to be more closely associated with those over 65 years of age,11 the situation is not going to improve any time soon.

It is for this reason that there is an urgent need for research into new treatments for heart failure.

References