

Congestive Heart Failure

What is congestive heart failure?

Congestive heart failure (CHF) is defined as the inability of the heart to pump a sufficient volume of blood to meet the body's requirements. Breathlessness and fatigue are its most common symptoms, along with swelling of the ankles and legs, as a result of retained fluid. CHF is often a consequence of some other disease which has damaged the heart, such as coronary artery disease, hypertension, a prior heart attack, heart valve or muscle disease, or severe lung disease. Fluid retention in the lungs and body in heart failure may lead to other complications such as kidney damage.

Initially, as the heart weakens, the body tries to compensate for its reduced output by producing a variety of so-called 'neurohormones' including noradrenaline, angiotensin 2, aldosterone, endothelins, antidiuretic hormone (vasopressin), natriuretic peptides, and cytokines, including pro-inflammatory cytokines such as interleukin 1(IL-1), IL-6 and tumour necrosis factor alpha.

In the longer term, however, this reaction further damages the heart, leading to progressive changes in heart structure and function, known as remodelling, that can ultimately be fatal. Newer medical therapies for heart failure attempt to interrupt this neurohormonal response, stop disease progression and lower mortality, as well as providing the symptomatic relief important for quality of life.

Who does congestive heart failure affect?

Recent screening studies in European member states showed that approximately three per cent of adults aged 45 or over had definite or probable heart failure. The incidence of heart failure rises steeply with age and men are more likely to be affected than women, especially below the age of 65.

Survey data from different populations suggests that the overall prevalence of congestive heart failure in persons 75 years of age and older is about 9-10 per cent. It is believed, that the sharp increase is partially the result of age-related changes in the cardiovascular system which compromise cardiac function.

As changes become more prominent and interact with atherosclerotic heart disease, valve stenosis, hypertension, and other cardiac diseases common in the elderly, the incidence of CHF increases sharply. Between 50 and 60 per cent of people admitted to hospital with CHF die within five years. It is estimated that CHF is responsible for over 600,000 admissions to hospital and 55,000 deaths in the European Union.

Congestive Heart Failure occurs when the heart cannot pump enough blood to meet the needs of the body. It kills many people every year. A variety of medicines has been developed to treat it, but more are still needed. Many approaches are being explored and trials are underway with a variety of new agents that may help people live longer and with a better quality of life.



Present treatments:

European guidelines for the treatment of CHF have recently been published and recommend initial use of ACE (angiotensin converting enzyme) inhibitors, often together with a diuretic, to control water retention and adverse neurohormonal response. Later, under specialist supervision, these may be combined with one of the adrenergic beta-blockers, which have been shown to be effective in lowering mortality in CHF.

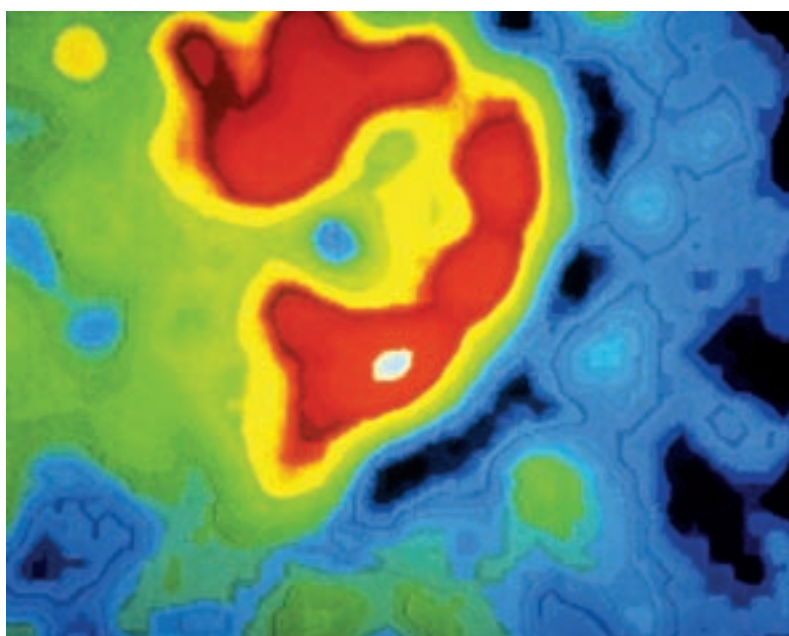
If this triple therapy is not sufficient, another diuretic, known as spironolactone, may be added. Despite encouraging results with the combination of these agents, mortality remains high and there continues to be a need for better therapies.

Angiotensin 2 receptor blockers (ARBs) - first developed for hypertension - are an alternative because of their ability to damp down neurohormonal pathways involving angiotensin. They are used in patients with CHF who may experience secondary effects with ACE inhibitors. Adding an ARB to current therapy was found to reduce hospitalisation due to CHF and to improve functional ability and quality of life, although overall mortality was not affected.

What's in the development pipeline?

Because heart function and cardiac remodelling involve a great many processes, many approaches are represented in the research pipeline for heart failure. For example, inflammatory cytokines directly reduce the ability of the heart muscle to contract, worsening its pumping ability, but also activate the renin-angiotensin-aldosterone-system (RAAS), causing narrowing of blood vessels and increasing the resistance against which the heart must pump.

Lipid-lowering medicines known as statins have anti-inflammatory properties and improve the function of the cells lining blood vessels, increasing nitric oxide levels, causing blood vessels to relax, and inhibiting platelet activation, all of which are seen in heart failure. Studies with statins are underway in patients with heart failure to see whether they can reduce death rates. Also, researchers are running a study with a renin inhibitor, since the compound affects the first step in RAAS activation and may therefore slow remodelling more effectively than ACE inhibitors or ARBs, which act later in the pathway.



Heart cells

Scientists also look into vasopeptidase inhibitors. These compounds inhibit both ACE and the neutral endopeptidase that breaks down bradykinin and natriuretic peptides. They may thus increase the excretion of sodium in the urine, lower vascular tone, and hence blood flow resistance. It may also inhibit smooth muscle cell proliferation which is part of life-endangering cardiac remodelling.

Other approaches focused on the neurohormones are currently being explored. A vasopressin V_{1A} and V_2 receptor antagonist has been shown to reduce water retention. There is another specific V_2 receptor antagonist at the Phase 2 stage. A selective aldosterone receptor antagonist has reached Phase 3 trial, and an endothelin synthesis inhibitor has moved to Phase 2 trial.

Compounds affecting other processes that are under study at the phase 2 stage include inhibitors of the adenosine A_1 receptor which can be considered a new type

of diuretic - a class of medicine that has otherwise not been the focus of much recent development; a thyroid hormone analogue which improves cardiovascular function; the molecule glucagon-like peptide-1, for raising exercise capacity; and a calcium-modulating agent to improve heart muscle function.

When the body can no longer compensate for the adverse changes in heart failure, a sudden worsening in condition known as acute decompensated heart failure may develop, requiring hospitalisation. Few medications are available for treating this condition, which is associated with high death rates.

New agents have reached Phase 3 trial. One is an intravenously administered calcium-sensitiser that increases the ability of heart muscle to contract and dilates blood vessels. Another is a peptide that has shown evidence of being able to reduce breathlessness. Following behind these, at Phase 2, are compounds which are designed to help reduce fluid retention in the lung.

The longer-term future:

As there is evidence that inflammatory mediators contribute to development and progression of CHF, researchers are studying non-specific immunomodulation therapy in patients with the disease. First reports suggest that genotyping of patients may be the crucial issue as non-specific immunomodulation resulted in better outcomes in a large segment of the heart failure population. If this proves to be so, then research will be needed to find the best combination of medications to use, as it is clear that monotherapy will not be viable.

More speculatively, therapy other than medicines may also have a role to play in CHF in the future, with a recent report of attempted cellular therapy with precursors of muscle cells taken from other parts of the body that could actively repair the damaged heart. Gene therapy has been used to insert an inhibitor for the enzyme beta-adrenergic kinase into heart cells, enabling them to contract more strongly. However, such approaches are still very experimental.

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