The management of congestive heart failure

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Summary

Despite the remarkable advances in cardiovascular therapeutics over the past four decades, little impact has been made on either the incidence or mortality rate of congestive heart failure and it remains a major clinical and public health problem. Recent practice audits have suggested that proven efficacious therapies are not maximally applied in patients with this condition. An approach to the patient with congestive heart failure is presented, emphasizing the two distinct syndromes of systolic dysfunction and diastolic dysfunction. Treatment recommendations are derived from consideration of the underlying pathophysiology and the evidence from randomised clinical trials.

Keywords: congestive heart failure, management

Aetiology of chronic congestive heart failure

Systolic dysfunction

- myocardial ischaemia and/or infarction
- mitral or aortic regurgitation
- dilated cardiomyopathy

Diastolic dysfunction

- hypertension
- myocardial ischaemia and/or infarction
- mitral or aortic stenosis
- hypertrophic obstructive cardiomyopathy
- restrictive cardiomyopathy
- pericardial disease

Box 1

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Pathophysiologically, congestive heart failure (CHF) is characterised by the inability of the heart "to pump blood at a rate commensurate with the requirements of the metabolizing tissues and/or to be able to do so only from an elevated filling pressure".¹ This results in a complex clinical syndrome with multiple organ involvement, manifesting in a multitude of symptoms and physical signs.

Epidemiology

CHF, with a prevalence of 1–2% in the general population,² is a major clinical and public health problem. The Framingham Heart Study has shown that CHF is more common in men than women, and that the incidence increases dramatically with age. Data from this study revealed that while there are only three cases per 1000 males aged 50 to 59 years (and two cases per 1000 females of the same age), there are 27 cases per 1000 males older than 80 years (and 22 per 1000 age-matched females).³ Despite major advances in the treatment and prevention of cardiovascular disease over the past 40 years, the incidence of CHF has changed very little and the prevalence has increased.³ Given the success of new therapies for myocardial infarction and other cardiac diseases, and the ageing demographics of our society, it is likely that the incidence and prevalence of CHF will continue to increase in the future.

CHF is associated with significant morbidity and mortality. Analysis of the SOLVD registry database suggests that up to 40% of newly diagnosed CHF patients are hospitalised within one year.⁴ The Framingham Study reported five-year survival rates of only 25% in males and 38% in females.³ Survival data from the control groups of patients in the major clinical trials of CHF reveal that mortality is directly related to the severity of functional impairment and left ventricular dysfunction. For instance, the six-month survival was only 45% in the control group of the CONSENSUS Trial⁵ which studied patients with severe (New York Heart Association (NYHA) Class IV) CHF. In the SOLVD trial, which enrolled patients with less severe symptomatology (NYHA Classes II and III), 60% of the control group were still alive after 3.5 years.⁶ Data from the latter study also clearly showed the inverse relationship between baseline ejection fraction and subsequent survival.

The mortality rates for CHF have changed little in the past four decades.³ This is despite the explosion in knowledge about the pathophysiology of CHF and the establishment, by randomised clinical trials, of some highly efficacious and readily available therapies for the condition. Although this may be partly attributable to a higher proportion of older, and sicker, patients in recent years, practice audits have revealed that the proven beneficial therapies are not maximally applied. For instance, a pattern of practice analysis carried out in eight Canadian centres showed that only 53% of patients with CHF were prescribed an angiotensin-converting enzyme (ACE) inhibitor.⁷ Moreover, recent market research in the UK revealed that, even when ACE-inhibitors are prescribed, much lower doses are being used than were evaluated in the clinical trials (42% of enalapril prescriptions were for 5 mg/day or less, and 75% of captopril prescriptions were for 75 mg/day or less).⁸

Aetiology of CHF

Although the Framingham data³ suggested that hypertension was the most common antecedent condition in patients who developed CHF, cross-sectional data from recent clinical trials indicate that CHF is now predominantly ischaemic in origin. In fact, ischaemic heart disease is the underlying cause in approximately 70% of all newly diagnosed heart failure patients and hypertension alone appears to account for only 15% of cases.^{6,9} The most common causes for impaired left ventricle function are listed in box 1.

Acute precipitants of heart failure

- Cardiac
- acute ischemic events (myocardial infarction, unstable angina)
 - arrhythmias
 - acute aortic/mitral regurgitation
- Systemic
- increased metabolic demands (anaemia, infection, fever, thyrotoxicosis, pregnancy, fluid overload, acute hypertension, post-operative state, stress)
 - alcohol excess
 - non-compliance with medications or diet
 - pulmonary embolism
 - interfering medications: NSAIDs, corticosteroids, negative inotropes (beta blockers, non-dihydropyridine calcium channel blockers, anti-arrhythmics), tricyclic antidepressants

Box 2

In evaluating the patient with presumed CHF, the clinician should perform a detailed history and physical examination to exclude other causes for the patient’s symptoms and to determine the underlying aetiology of the heart failure. In addition, the clinician should search for the acute precipitants (box 2) which led to the patient’s presentation at that point in time.

Systolic vs diastolic dysfunction

Although heart failure patients with systolic dysfunction and those with primarily diastolic dysfunction may exhibit similar symptoms and signs, the differentiation between the two syndromes has important therapeutic and prognostic implications. Certainly, different pathophysiologic processes underlie the two syndromes and compensatory neuro-endocrine activation appears to be largely seen in those patients with systolic dysfunction. Systolic dysfunction is characterised by reduced left ventricular contractility for the degree of preload, and manifests in a reduced left ventricular ejection fraction (LVEF). On the other hand, the fundamental problem in patients with diastolic dysfunction is impaired ventricular relaxation and decreased compliance in diastole. As a result, patients with diastolic dysfunction usually have normal LVEF but increased left atrial pressures, and chamber pressures increase markedly in response to increases in left ventricular volume.

While most patients exhibit features of both systolic and diastolic dysfunction, systolic impairment is the predominant defect in the vast majority. The reported prevalence of predominant diastolic dysfunction varies from 10–30% in the literature.¹⁰ In general, ischaemic heart disease is the commonest reason for systolic dysfunction while left ventricular hypertrophy, secondary to hypertension or valvular abnormalities, accounts for the majority of diastolic dysfunction.

Although left ventricular systolic function can only be accurately determined with imaging tests (echocardiography, radionuclide or radiographic ventriculography) the clinician can glean clues as to the underlying syndrome from a careful history, physical examination, and screening tests such as electrocardiogram (ECG) and chest X-ray. As systolic dysfunction is usually associated with prior myocardial infarction and dilation of the left ventricle, suggestive clinical features include displacement of the apex, a third heart sound, enlarged cardiac shadow on the chest X-ray, and Q waves on the ECG. On the other hand, those conditions associated with diastolic dysfunction usually do not lead to significant cardiac enlargement and the only clues may be a normal heart size on chest X-ray and the presence of left ventricular hypertrophy on physical examination (sustained apex, fourth heart sound) or ECG. Since knowledge of the extent of systolic and diastolic dysfunction directs further investigation and therapy, some assessment of left ventricular function should be done in all patients presenting with CHF.

Evaluation of the patient with CHF

The evaluation of patients presenting with CHF includes a careful history and physical examination (figure). Additional investigations should include a full blood count, electrolytes, creatinine, chest X-ray, and ECG. In addition, an objective assessment of LVEF would be useful in all patients with new-onset CHF. The decision to proceed to further investigations, such as exercise stress test or coronary angiography, should be dictated by the circumstances of the specific case.

In following patients with CHF, the NYHA functional classification (box 3) has been proven to be a useful and reproducible tool and allows clinicians to communicate the severity of a patient’s symptoms accurately. In addition, the monitoring of weight, blood pressure, and heart rate provides important clues as to the status of the patient.

Treatment of CHF

The first steps in the management of a patient with CHF include determination of the underlying aetiology and the recognition and treatment of any acute precipitants. As with any chronic disease, education and counselling of the patient and family members about CHF, the goals of treatment, and the need for compliance with diet, fluid restriction and medications plays an important role. In addition, patients with CHF should be advised to avoid substances which may exacerbate their condition, such as nonsteroidal anti-inflammatory drugs or alcohol. From a public health perspective, the identification and treatment of conditions that may lead to CHF, such as hypertension or ischaemic heart disease, is an important initiative.

NYHA functional classification for CHF

Class	Symptoms
I	no limitation of physical activity
II	dyspnoea or fatigue with ordinary physical activity
III	dyspnoea or fatigue with less than ordinary physical activity
IV	dyspnoea or fatigue at rest

Note: ordinary physical activity defined as walking two blocks on the level or climbing one flight of stairs

Box 3

Figure Treatment of CHF – a summary algorithm (adapted with permission from the Clinical Quality Improvement Network Investigators⁷)

NON-PHARMACOLOGIC THERAPY

All patients with heart failure should be placed on a low-sodium diet, with the degree of salt restriction dependent on the severity of heart failure. For the majority of CHF patients, a no-added-salt diet (2–3 g sodium per day) is sufficient. Stricter salt restrictions may have to be instituted in patients with refractory symptoms. Restriction of fluids to 48 fluid ounces per day is usually sufficient for most patients, but the fluid restriction should be increased in those patients with hyponatraemia or symptoms refractory to diuretic therapy. The fluid restriction may result in an uncomfortable sensation of thirst; this should be explained to the patient and advice should be given about measures to quench the thirst (such as mints or lozenges). Exercise training may be beneficial in CHF,¹¹ and patients should be encouraged to do regular, light aerobic exercise.

PHARMACOLOGIC THERAPY

The choice of pharmacologic therapy in CHF depends on whether the patient exhibits primarily systolic or diastolic failure.

Systolic dysfunction

The agents currently employed in the treatment of systolic heart failure include diuretics, ACE-inhibitors, digoxin, and nitrates. Consideration of the Frank Starling curve allows one to deduce the probable effects of interventions in these patients. Agents which reduce preload, such as diuretics, reduce pulmonary and peripheral oedema but have little impact on stroke volume. Agents which decrease afterload or increase left ventricular contractility can lead to improvements in systolic function.

Diuretics Although diuretics relieve pulmonary and peripheral congestion, they may also lead to electrolyte disturbances, enhanced neurohormonal activation, and reduced cardiac output in patients with systolic failure. There is no evidence that they improve survival in patients with CHF, and they are now rarely used as single agents. However, the patient presenting with fluid overload will require a diuretic initially and the choice between a loop diuretic or a thiazide depends on the degree of fluid overload and the patient's renal function (thiazides have greatly reduced efficacy in the setting of renal failure). In those patients with refractory fluid overload despite high doses of loop diuretics, the addition of agents which act on different segments of the nephron, such as thiazides or metolazone, may help induce a brisk diuresis.

After initial stabilisation, the minimum diuretic dose should be used that maintains euvolaemia. Patients on chronic diuretic therapy should have their serum electrolytes, magnesium, and renal function monitored regularly. We recommend that diuretics be prescribed as a single dose in the morning as much as possible and that routine potassium supplementation be employed

unless regular testing demonstrates it unnecessary. By and large, potassium-sparing diuretics should be used cautiously in patients on ACE-inhibitors.

ACE-inhibitors Over the past decade, numerous trials have clearly established ACE-inhibitors as the agents of first-choice in the treatment of systolic CHF, for both symptomatic and asymptomatic patients (table). In two large randomised clinical trials, symptomatic patients, with NYHA Class II–IV failure, demonstrated reduced total and cardiac mortality, decreased hospitalisations, and improved exercise tolerance when treated with ACE-inhibitors.^{5,6} In asymptomatic patients with reduced left ventricular systolic function, hospitalisations and the progression to overt CHF were reduced by ACE-inhibitors.¹² In addition, ACE-inhibitors have been shown to reduce hospitalisations for CHF and acute coronary events (fatal and non-fatal) in patients with reduced left ventricular function and NYHA Class II–IV failure or recent myocardial infarction.^{13–15} Other clinical trials have shown that ACE-inhibitors, when given to all patients in the post-infarction period, can reduce cardiovascular mortality and hospitalisations for CHF.^{16–18}

The beneficial effects of ACE-inhibitors are thought to be secondary to afterload reduction and amelioration of neurohormonal activation. As the benefits of ACE-inhibitors appear to be a consistent class effect, the choice of specific agent should be based on the duration of action and cost. Although the dose required for maximal therapeutic efficacy is not known, clinical trials have generally employed high-dose ACE-inhibition (20 mg of enalapril, 150 mg of captopril, and 10 mg of ramipril). While hypovolaemic patients may develop symptomatic and troublesome hypotension with ACE-inhibitor therapy, euvolaemic or fluid-overloaded patients tend to tolerate these agents well. Thus, patients exhibiting significant hypotension with an ACE-inhibitor should have the dose of their diuretic reduced. As ACE-inhibitors exhibit their greatest benefits in patients at highest risk for subsequent deterioration, they should not be withheld from elderly patients or those with renal insufficiency, although the doses used should be individually adjusted to less than the usual recommended doses.

Other vasodilators While the first Veterans Affairs Heart Failure Trial (V-HeFT I) reported that combination therapy with hydralazine and isosorbide dinitrate improved exercise tolerance and reduced mortality in patients with moderate to severe systolic dysfunction (NYHA Class II–III),¹⁹ questions about the statistical validity of the trial have been raised.²⁰ Certainly, the subsequent V-HeFT II trial²¹ suggested that survival benefits were greater with enalapril than the hydralazine/isosorbide dinitrate combination. As a result, hydralazine/isosorbide dinitrate is now recommended only for those patients unable to tolerate ACE-inhibitors (due to renal dysfunction, hyperkalaemia, hypersensitivity, or persistent cough). There is no evidence that the other direct vasodilators, such as prazosin and minoxidil, provide any benefits in heart failure. The first generation calcium channel blockers (nifedipine, diltiazem, and verapamil) should be avoided as they have negative inotropic effects and

Table Summary of major ACE-inhibitor trials in CHF

<i>Trial</i>	<i>Study drug</i>	<i>Patients</i>	<i>Results</i>
<i>Reduction of hospitalisations for CHF</i>			
SOLVD Prevention ¹²	enalapril	asymptomatic LVEF<35%	47% reduction
SOLVD Treatment ⁶	enalapril	NYHA II-III LVEF<35%	26% reduction
SAVE ¹³	captopril	post-MI LVEF<40%	25% reduction
<i>Reduction of mortality</i>			
CONSENSUS I ⁵	enalapril	NYHA IV	36% reduction
SOLVD Treatment ⁶	enalapril	NYHA II-III EF<35%	16% reduction
SOLVD Prevention ¹²	enalapril	Asymptomatic LVEF<35%	8% reduction (NS)
SAVE ¹³	captopril	post-MI LVEF<40%	19% reduction
AIRE ¹⁴	ramipril	post-MI with CHF	25% reduction
CONSENSUS II ¹⁵	enalapril	post-MI	8% excess (NS)

Abbreviations: LVEF= left ventricular ejection fraction; NS=not statistically significant; MI= myocardial infarction

there is emerging evidence that they may increase mortality in cardiac patients.^{22,23} The recent PRAISE trial²⁴ reported that a second-generation calcium channel blocker, amlodipine, significantly reduced mortality when added to usual therapy (including ACE-inhibitors) in patients with non-ischaemic dilated cardiomyopathy (and exhibited a neutral effect in patients with ischaemic disease). However, the newer calcium channel blockers have been inadequately studied and cannot yet be recommended for routine use.

Digoxin Digoxin is a positive inotrope which reduces neurohormonal activation and inhibits AV nodal conduction. While it is strongly recommended in patients with coexistent systolic dysfunction and atrial fibrillation, its role in the treatment of patients with CHF and sinus rhythm has been hotly debated. Certainly, withdrawal studies have demonstrated that the discontinuation of digoxin leads to clinical deterioration in patients with sinus rhythm and heart failure who had been stable on digoxin pre-trial.^{25,26} The Digitalis Investigation Group recently reported that the addition of digoxin to the treatment regimen of patients with systolic dysfunction (the majority of whom were taking an ACE-inhibitor) led to a significant reduction in deaths and hospitalisations due to worsening heart failure, but no change in overall mortality.²⁷ Based on the trial evidence, digoxin would appear to have a role as a third-line agent for symptom relief in those patients with sinus rhythm and systolic heart failure refractory to ACE-inhibitors and diuretics.

Other inotropes Although the intravenous inotropes dobutamine and dopamine do improve the short-term haemodynamic profile in patients with systolic CHF, they do not improve long-term survival and have a limited role in the management of CHF outside critical care areas or specialised clinics. The results from the clinical trials evaluating the phosphodiesterase inhibitors and beta agonists have been disappointing; in fact, a meta-analysis of 21 randomised clinical trials of these drugs in CHF revealed a 76% excess risk of death (95% confidence intervals 27–144% excess risk) in the active treatment groups compared with the placebo groups.²⁸ The large PROMISE Trial²⁹ published subsequently confirmed the finding of excess mortality in milrinone-treated patients. Although a recent trial³⁰ suggested that low-doses of vesnarinone, a sodium pump inhibitor with mild phosphodiesterase inhibitor activity, may reduce symptoms and mortality in systolic CHF, there was excess mortality with higher doses and this agent must be considered experimental until further confirmatory studies are completed.

Beta-blockers Despite their negative inotropic effects, the ability of beta-blockers to reduce neurohormonal activation, myocardial ischaemia, and ventricular arrhythmias provides some rationale for their use in systolic CHF. The inconclusive results of the trials evaluating beta-blockers in CHF do not support a recommendation for their widespread use. However, low-dose beta-blockade (metoprolol 5–50 mg bid), in addition to standard therapy with ACE-inhibitors, digoxin, and diuretics, has been shown to significantly improve ejection fractions and exercise tolerance, and reduce death/cardiac transplantation in patients with idiopathic, non-ischaemic dilated cardiomyopathy.³¹ The precise role of beta-blockers in CHF remains to be answered by ongoing clinical trials. Recent studies on a beta-blocker with vasodilator properties, carvedolol, suggest that substantial benefit can be gained with this agent but its role in routine practice remains to be defined.³²

Anti-arrhythmic therapy Anti-arrhythmic therapy is not recommended for CHF patients with asymptomatic arrhythmias, given the increased mortality seen in the anti-arrhythmic trials of the mid-1980s. In patients with symptomatic or life-threatening arrhythmias (sustained ventricular tachycardia or ventricular fibrillation), the type III anti-arrhythmic drugs amiodarone, and perhaps sotalol, are the agents of first-choice. While the GESICA trial³³ did demonstrate improved survival with the addition of amiodarone to standard therapy in patients with systolic CHF (with and without symptomatic arrhythmias), another recent trial³⁴ failed to do so. Thus, amiodarone cannot yet be recommended for routine use in CHF patients without symptomatic arrhythmias.

Anticoagulation Warfarin prophylaxis is clearly appropriate for most patients with coexistent CHF and atrial fibrillation.³⁵ Although there is a paucity of clinical trials evaluating the role of anticoagulants in patients with CHF and sinus rhythm, we believe that, in the absence of clear contraindications, warfarin anticoagulation (with a goal PT INR of 2–3) is appropriate for patients with

dilated, poorly functioning left ventricles or with evidence of intracardiac thrombus on echocardiography.

Treatment of myocardial ischaemia Ischaemic events are common causes of clinical deterioration in previously stable patients with CHF and the management of myocardial ischaemia is an important issue in CHF.³⁶ ACE-inhibitors have been shown to reduce the incidence of angina and myocardial infarctions in treated patients, and any patients with coexistent CHF and angina should be aggressively treated to prevent further deterioration in cardiac function. It should be noted that chest discomfort may be due to ventricular dilation and elevated filling pressures rather than ischaemia, and noninvasive testing (with exercise stress test or thallium scanning) may be advisable prior to embarking on therapy.

Therapy with long-acting nitrates does reduce preload and anginal symptoms, although there is no evidence that it affects survival. In fact, at least one trial has suggested that surgical revascularisation may be more beneficial in patients with significant ischaemia and CHF than medical therapy.³⁷ Given the relatively high rate of peri-operative complications in these patients and the burden of coexistent disease, we believe that medical therapy should be the first step in patients with significant angina and CHF, although possible revascularisation should not be ruled out.

Diastolic dysfunction

As the majority of the patients in the heart failure trials have had systolic failure, there is a dearth of clinical trial data regarding treatment options for diastolic dysfunction. Given the fundamentally different pathophysiologic processes underlying diastolic dysfunction, the goals of therapy differ from those in systolic dysfunction. In fact, central to the treatment of this condition are efforts to improve the compliance of the left ventricle and increase diastolic filling. For example, diastolic dysfunction may predominate during myocardial ischaemia and therefore anti-ischaemia therapy is the appropriate treatment.

For those conditions associated with left ventricular hypertrophy, treatment of the underlying condition (such as antihypertensive therapy for hypertension or surgery for valvular abnormalities) may lead to regression of hypertrophy and improved diastolic function. In addition, surgical treatments for pericardial disease and hypertrophic obstructive cardiomyopathy have been shown to improve cardiac function. However, in some cases, such as the restrictive cardiomyopathies, treatment of the underlying condition is not possible and the clinician must pursue other options.

Isovolaemic relaxation is an energy-dependent process, and the non-dihydropyridine calcium channel blockers verapamil and diltiazem have been shown to improve some parameters of diastolic function by altering the calcium flux in the myocardium.¹⁰ However, there is as yet no evidence that they reduce clinical endpoints (such as death or hospitalisations) in these patients. Another means of improving ventricular filling, and thus diastolic function, is to prolong diastole. Although there are no clinical trials assessing their efficacy, the beta-blockers and non-dihydropyridine calcium channel blockers would seem to be the best agents for this task.

Conclusion

CHF is an increasingly important condition in our society. Disturbingly, the morbidity and mortality of CHF have not declined significantly in the past 40 years. However, intensive research in the past decade has identified therapies which do significantly impact on clinical endpoints such as death and hospitalisation. New therapies, such as angiotensin II receptor antagonists, and new applications of currently available therapies such as beta-blockers, are under evaluation and the clinician will probably continue to see a constant expansion in the therapeutic armamentarium for this condition.

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