Diastolic heart failure in older people – myth or lost tribe?

AJ Baxter and CS Gray

ABSTRACT – Left ventricular diastolic dysfunction occurs due to a variable combination of abnormal myocardial relaxation and reduced ventricular compliance. The diagnosis of diastolic congestive heart failure is controversial. Some studies suggest that up to one-third of older people with symptomatic congestive heart failure (CHF) have echocardiograph evidence of diastolic dysfunction. Other authors have suggested the comorbid diseases often found in persons with suspected diastolic CHF explain the patient's symptoms and hence diastolic CHF is a misdiagnosis in many cases. Many of the characteristic echo features of diastolic dysfunction occur in normal ageing hearts. Unlike in systolic CHF, evidence for disease modifying treatment is lacking. Clinical trials currently in progress to determine the effectiveness of ACE inhibitors and angiotensin II receptor antagonists in the management of diastolic CHF may clarify the prognosis and management of this condition.

KEY WORDS: congestive heart failure, diastole, left ventricular dysfunction

Background

The management of patients with congestive heart failure (CHF) has long been the domain of elderly care physicians although their contribution to the care of this group of patients is often under-recognised. CHF remains predominantly a disease of older people with the prevalence rising exponentially over the age of 60 years[1–4]. New cases present at a mean age of 76 years, are more commonly male and have coronary artery disease as the most the likely aetiology[1].

Although the management of CHF with left ventricular systolic dysfunction has been clarified through large clinical trials that have established a range of effective interventions, older patients were underrepresented in these trials. Only one-third of patients in the recent CHF β-blocker trials were aged over 70 years with the overall mean under 65 years[5,6]. Patients with comorbid disease, which is often the norm in the elderly, are invariably excluded from clinical trials. As a result, the day-to-day management of patients with CHF is often based upon extrapolations from existing evidence gained from a younger population, with a low prevalence of multisystem disease.

Whilst an evidence base supports the management of systolic CHF, there is an additional group of patients with symptomatic CHF for whom there is at present no evidence to guide management. These individuals have clinical evidence of CHF, have a good therapeutic response to diuretics and yet transthoracic echocardiography demonstrates preserved ventricular systolic function. The group are usually labelled as having diastolic CHF. Guidelines exist for the diagnosis of diastolic CHF[7], but many of the echo characteristics suggested also occur in normal ageing hearts, leading to diagnostic uncertainty. This uncertainty, when combined with the limited evidence for therapeutic intervention, has recently led some authors to suggest that in many cases diastolic dysfunction may represent a misdiagnosis[8].

Does this group represent a diagnostic myth, or are they a lost tribe with unrecognised symptomatic CHF for whom there is, as yet, no clinical trial evidence to direct management? In this paper we review the epidemiology, pathophysiology, diagnosis and treatment of CHF due to diastolic dysfunction.

What is diastolic dysfunction?

Left ventricular diastole occurs between aortic and mitral valve closure. At the beginning of diastole there is a period of isovolumetric relaxation. This occurs in the interval immediately following closure of the aortic valve and before the opening of the mitral valve. During this time left ventricular pressure declines rapidly but no change in volume occurs. Following mitral valve opening, ventricular filling is rapid until atrial and ventricular pressures equalise – termed 'diastis'. Filling then continues due to the momentum of venous return to the atrium and the contribution of atrial systole.

Diastolic dysfunction occurs due to a variable combination of abnormal myocardial relaxation and reduced ventricular compliance. At a cellular level, prolonged binding of calcium to troponin leads to myocyte dysfunction and failure of normal relaxation.

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This slows the rate of fall in left ventricular pressure and thus prolongs isovolumetric relaxation time. In the longer term, ventricular compliance is further decreased by collagen deposition in the myocardium. As a consequence of abnormal relaxation and reduced compliance, ventricular filling is slow or incomplete unless left atrial pressure rises. Acute or chronic elevations in left atrial pressure results in pulmonary and systemic venous congestion causing the clinical syndrome of CHF.

How large is the lost tribe, or is diastolic CHF a misdiagnosis?

Heterogeneity in the reported populations and diagnostic criteria has led to uncertainty regarding the true prevalence and natural history of this condition. North American studies have suggested that around 30% of older patients with apparent heart failure have diastolic CHF[9–13]. In one series, 25% of patients aged over 75 admitted with symptomatic CHF to a North American hospital had ejection fractions greater than 50%, increasing to 49% of patients aged over 85[9]. No equivalent studies have been performed in older persons in the UK, but large population studies have estimated the prevalence to be much lower, at around 15%[14].

Recent UK studies have suggested that the label of diastolic CHF may be a misdiagnosis in many patients. Patients with suspected CHF have a high incidence of atrial fibrillation, ischaemic heart disease, chronic obstructive pulmonary disease and obesity. If symptoms and signs are attributed to these conditions then isolated diastolic dysfunction as a diagnosis may occur in only 7% of patients with suspected CHF[8]. However, comorbidity is often the norm rather than exception in older people and whilst it is important to identify and fully address these comorbid diseases with appropriate treatment the relative contribution of cardiac and non-cardiac disorders to a patient's symptom complex remains unclear.

What causes diastolic CHF?

In both systolic and diastolic CHF the most common associated aetoiologies are increasing age, coronary artery disease, hypertension and diabetes mellitus[4,9].

Diastolic CHF and ischaemic heart disease

Diastolic CHF may occur in patients with symptomatic or asymptomatic coronary artery disease as the result of a number of mechanisms. In the normal ventricle, myocardial relaxation is controlled by Ca^{2+} uptake by the sarcoplasmic reticulum and also Ca^{2+} efflux from myocytes. This process is mediated by sarcoplasmic reticulum adenosine triphosphatase (ATPase). Myocardial ischaemia causes ATP depletion and hence inhibits ventricular relaxation. Ischaemia also decreases intrinsic myocardial compliance. This is further exacerbated if infarction occurs with subsequent scar formation, fibrocellular infiltration and myocardial contracture[15].

Diastolic CHF and hypertensive heart disease

Abnormalities of left ventricular diastolic filling have been noted in adult hypertensives[16]. Hypertension causes diastolic CHF through both coronary artery disease, described above, and left ventricular hypertrophy (LVH). In LVH there is an increase in left ventricular mass[17], reduced diastolic compliance and reduced ventricular relaxation, which can be mediated by subendocardial ischaemia[18,19]. LVH can also predispose to myocardial fibrosis[20].

Diastolic CHF and diabetes mellitus

The Framingham study demonstrated that the risk of developing CHF is substantially increased in diabetes mellitus. This is partially mediated by coronary artery disease but other mechanisms are also important. In diabetic subjects with CHF who have no histological evidence of large or small vessel disease, the most common histological abnormality is myocardial fibrosis[21]. This, together with increased collagen deposition[22], and abnormal myocardial Ca^{2+} handling[23], can predispose to diastolic CHF.

Diastolic CHF and atrial fibrillation

It is generally accepted that diastolic CHF is often associated with atrial fibrillation[9]. To maintain ventricular filling in the presence of a stiff left ventricle, left atrial pressure rises. This may lead to increased left atrial size and increased risk of atrial fibrillation[24]. The onset of atrial fibrillation may precipitate worsening of clinical features.

How can a diagnosis of diastolic congestive cardiac failure be established or excluded?

Heart failure is difficult to diagnose on clinical grounds alone[25,26]. Clinical features that lead to a suspected diagnosis of CHF should be investigated, normally with a transthoracic echocardiograph. What if the echocardiograph shows preserved left ventricular function in the presence of typical CHF symptoms? Should the clinician make a diagnosis of diastolic left ventricular dysfunction or attribute the symptoms or signs to other pathology? A clinician can be guided by the transthoracic echo result in suspected diastolic CHF.

Echocardiographic criteria for diastolic CHF

Diagnosing diastolic CHF by transthoracic echocardiography may be difficult, as many of the features of diastolic dysfunction can also occur in the 'normal' ageing heart. Various ejection fractions (all >40%) have been suggested[7,27,28], but measurement of ejection fraction (EF) is subject to variation within individuals and across populations where a normal distribution can be demonstrated[29,30]. LVH is associated with diastolic dysfunction, particularly in association with hypertension[31], but LVH can also be associated with 'normal ageing'[32].

Echocardiographic Doppler studies demonstrating a reversed

E:A ratio, and prolongation of the isovolumic relaxation time (IVRT) is the most universally accepted indicator of diastolic dysfunction. The E wave represents ventricular filling due to relaxation; the A wave represents flow into the left ventricle during atrial systole. In a normal functioning left ventricle, the majority of filling occurs during ventricular relaxation but in diastolic LV dysfunction abnormal relaxation reduces the E wave velocity and raised atrial pressure increases the A wave velocity. Hence E:A ratio is reversed in diastolic CHF. The IVRT represents the period between closure of the aortic valve and the start of the E wave. This is prolonged when ventricular relaxation is reduced and hence is a feature of diastolic CHF. However, both reversed E:A ratio and prolonged IVRT occur in the ageing as well as the failing heart and are unlikely to be sensitive enough to distinguish pathological diastolic dysfunction from normal ageing[33,34].

The European study group on diastolic heart failure has produced guidelines for the diagnosis of diastolic CHF that include age reference ranges for Doppler measurements in individuals aged over 50[10]. A single range spanning over 30 years for individuals aged between 50 and over 80 is unlikely to differentiate the Doppler flows that occur in diastolic left ventricular dysfunction and the normal ageing heart. Whilst the guidelines do represent a significant advance, the high-quality Doppler signals required are often difficult to obtain in older patients and many of the suggested echo criteria are not at present incorporated in routine transthoracic echocardiography. Reference ranges for normal Doppler values in older persons need to be established. Recent US guidelines acknowledge the difficulties of diagnosing diastolic dysfunction by echocardiography and suggest a definitive diagnosis can only be achieved at cardiac catheterisation[11].

What is the most effective treatment?

If diastolic LV dysfunction is likely to be the aetiology in a number of older persons with CHF, what then are the treatment options? At present there is no evidence base derived from randomised controlled trials to determine the optimum treatment aimed at reducing morbidity and mortality for patients with diastolic dysfunction. First line treatment should be aimed at comorbid conditions. Disorders such as chronic obstructive pulmonary disease, atrial fibrillation, and ischaemic heart disease, should be rigorously sought and appropriate treatment instituted. In cases associated with ischaemic heart disease, coronary revascularisation has been shown to improve diastolic dysfunction[35].

Specific therapies proposed for diastolic CHF include diuretics, calcium channel blockers, beta-blockers and angiotensin I-converting enzyme (ACE) inhibitors. Diuretics reduce ventricular filling pressures and pulmonary congestion, thereby relieving symptoms. Cardiac output in patients with diastolic dysfunction is very dependent on ventricular preload. This may fall with diuretic therapy and as a result patients may be very sensitive to these agents. They should therefore be started at a low dose and increased gradually. Both calcium channel blockers[36] and beta blockers[37] lower blood pressure and heart rate, and have been shown to decrease LVH. Whilst this may improve diastolic function, the impact of these agents on mortality and morbidity is unknown.

ACE inhibitors are potentially the most promising agents in the treatment of diastolic CHF but, unlike their use in the treatment of systolic CHF, their benefit remains uncertain. A small number of patients enrolled into CONSENSUS I (enalapril vs conventional management) had preserved left ventricular systolic function. In this group there was no benefit with ACE inhibitor compared to placebo[38]. In the VHEFT II trial (enalapril vs hydralazine/nitrates) there was a mortality benefit for ACE inhibitor treated patients with preserved left ventricular systolic function[39] but again the number involved was small. Two randomised placebo-controlled trials of patients with diastolic CHF are currently underway. In one arm of the CHARM study (Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity), patients with symptomatic CHF and an ejection fraction of >40% are randomised to the angiotensin II receptor antagonist candersartan or matching placebo. Outcome measures are mortality and hospitalisation[40]. The PEP-CHF study is a placebo-controlled trial, which seeks to determine the effects of the ACE inhibitor perindopril versus placebo in older patients with symptomatic CHF and diastolic dysfunction. Participants are over 70 years old and have EF >40% plus one or more of the following:

- left ventricular hypertrophy
- dilated left atrium
- Doppler indices of diastolic dysfunction at transthoracic echo.

Outcome measures are mortality and hospitalisation[41].

Key Points

Diastolic left ventricular dysfunction occurs as the result of a variable combination of abnormal myocardial relaxation and reduced ventricular compliance

The physiological changes of left ventricular diastolic dysfunction lead to increased left atrial pressure and thus pulmonary and systemic venous congestion causing the clinical syndrome of CHF

Many of the echocardiographic criteria for the diagnosis of diastolic dysfunction may be found in the normal ageing heart

The diagnosis of diastolic dysfunction is controversial. Some studies suggest that it is a common cause of CHF in older persons, while other authors suggest in many cases it is a misdiagnosis

Current treatment of patients with suspected diastolic CHF should reflect symptom relief for fluid overload and treatment of associated cardiovascular risk factors

Ongoing clinical trials may clarify the role of ACE inhibitors and angiotensin II receptor antagonists in improving mortality

Summary

CHF due to diastolic left ventricular dysfunction is a controversial area. We have reviewed the weight of studies outlining the pathophysiology. We have also discussed the difficulties in diagnosis, both on clinical grounds and by investigations, highlighting the debate as to whether many patients with suspected diastolic CHF do indeed have the condition or whether they are misdiagnosed and their symptoms explained by comorbid disease. We suggest that a number of older persons with suspected CHF do have diastolic LV dysfunction. The diagnosis of diastolic CHF should be based upon recent guidelines that should be incorporated into transthoracic echo examinations thus aiding echocardiographers to identify probable cases. Clinical trial evidence for the effectiveness of ACE inhibitors and angiotensin II receptor antagonists in the management of diastolic CHF may clarify the prognosis and management of affected patients, but in the meantime clinicians should focus on symptom relief from fluid overload and treatment of associated cardiovascular risk factors.

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