Diastolic heart failure
a clinical update

Although the clinical syndrome of heart failure is usually secondary to impaired left ventricular contraction, a significant number of patients with this syndrome have isolated diastolic dysfunction. Systolic and diastolic heart failure may be clinically indistinguishable; the mainstays of establishing a diagnosis of diastolic heart failure are noninvasive techniques, such as echocardiography.

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What is heart failure?

Heart failure is a pathophysiological state in which the heart as a pump fails to meet the needs of the metabolism in the tissues and/or can do so only with abnormally increased diastolic volume and/or pressure.

Classically, heart failure resulting in hospital admission is associated with systolic dysfunction of the left ventricle. The pathophysiology of systolic heart failure is well understood and the condition well recognised. Recently, diastolic dysfunction of the left ventricle has been more clearly characterised and identified to be of increasing importance, especially in the ageing population.

What is diastolic heart failure?

Pure diastolic heart failure is characterised by:

- signs and symptoms of congestive cardiac failure
- normal, or only mildly abnormal, left ventricular (LV) systolic function, and
- abnormal LV relaxation, filling and/or stiffness (Table 1).[1]

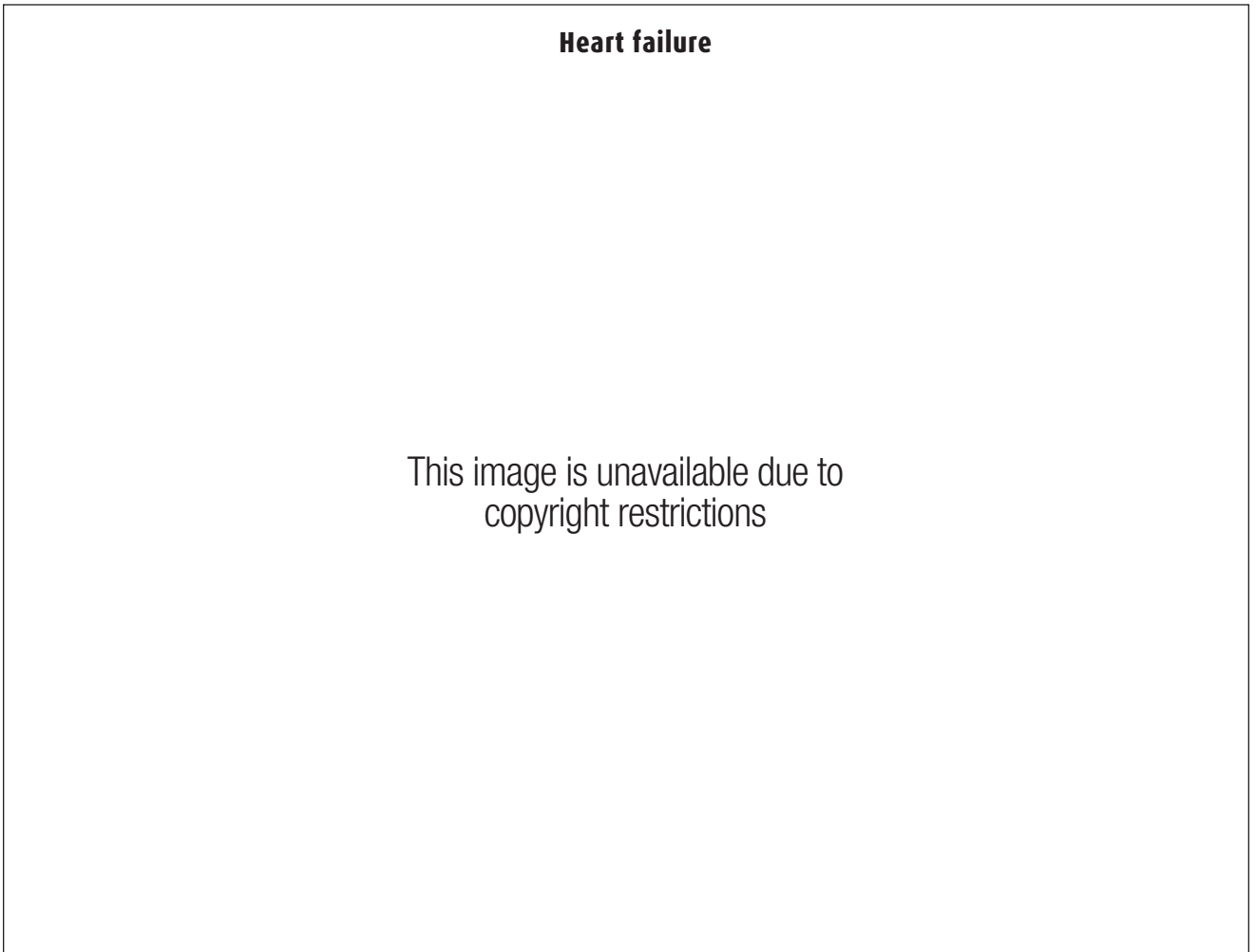
Does diastolic heart failure really exist?

A recent report concluded that most patients seen in general practice with symptoms of heart failure and preserved LV systolic function were misdiagnosed as having diastolic heart failure. Most of these patients had an alternative explanation for their symptoms, such as obesity or lung disease.[2] This emphasises that patients with dyspnoea and normal systolic function cannot be assumed to have diastolic heart failure. Thus, before diastolic dysfunction can be suspected, a diagnosis of congestive cardiac failure must be definite, normal systolic function documented, and alternative diagnoses excluded.[3]

IN SUMMARY

- **Although systolic and diastolic dysfunction heart failure coexist, a significant number of patients have pure diastolic heart failure.**
- **Pure diastolic failure is characterised by congestive cardiac failure, normal or almost normal systolic function, and abnormal left ventricular relaxation, filling and/or stiffness.**
- **Echocardiography is a useful tool for diagnosing diastolic dysfunction, demonstrating its aetiology, and excluding systolic left ventricular dysfunction.**
- **Treatment of pure diastolic heart failure, although empirical, requires addressing potential reversible processes, such as hypertension, atrio-ventricular synchrony, and ischaemia.**
- **It is important that lifestyle measures are not overlooked. These include restricted salt intake, avoidance of alcohol, regular physical activity and pneumococcal and influenza vaccinations.**

Heart failure



Pure diastolic heart failure is characterised by signs and symptoms of congestive cardiac failure, normal or only mildly abnormal left ventricular (LV) systolic function, and abnormal LV relaxation, filling and or/stiffness.

ILLUSTRATION: K. SOMERVILLE, CMSP

That diastolic dysfunction is a real entity has recently been confirmed in patients with hypertensive heart failure.[4] Researchers evaluated 38 patients with acute pulmonary oedema (confirmed on chest x-ray) and hypertension (systolic blood pressure >160 mmHg) in the absence of pneumonia, myocardial infarction and renal failure. During the acute episode of pulmonary oedema, half of the patients had normal systolic function and no mitral regurgitation, and the LV ejection fraction measured after treatment was unchanged. Importantly, diastolic function in these patients was abnormal as assessed echocardiographically by mitral inflow Doppler velocities.

Table 1. Features suggestive of diastolic heart failure

- Dyspnoea, orthopnoea, effort intolerance
- Gallop rhythm (S_4), tachycardia, crepitations, elevated jugular venous pulse
- Signs of valvular heart disease (e.g. aortic stenosis, mitral stenosis)
- Hypertension
- Pulmonary congestion with minimal, if any, cardiomegaly on chest x-ray
- Left ventricular hypertrophy on electrocardiography and/or echocardiography
- Normal left ventricular ejection fraction with or without abnormal diastolic indices on echocardiography

Table 2. Conditions associated with diastolic dysfunction

Condition	Possible contributory mechanism*
Coronary artery disease	Asynchronous myocardial relaxation secondary to ischaemia or scar and altered mechanical loading
Hypertensive heart disease	Left ventricular hypertrophy (LVH)
Valvular heart disease	Aortic stenosis leading to LVH, mitral stenosis leading to reduced filling
Normal ageing	Impaired early filling due to reduced compliance with associated increase in late (atrial systolic) filling
Hypertrophic cardiomyopathy	Hypertrophy, fibrosis, and asynchronous regional lengthening, hence impaired relaxation
Infiltrative disease of the myocardium (amyloid, sarcoid, hemochromatosis, lymphoma)	Reduced left ventricular end-diastolic distensibility (increased left ventricular end-diastolic pressure)
Diabetes mellitus	Interstitial accumulation of glycoproteins, myocardial fibrosis leading to impaired relaxation
Heart transplant	Multiple factors related to donor and recipient size mismatch, ischaemia, rejection episodes, cyclosporin-induced hypertensive LVH
Pericardial disease	Altered left ventricular filling

*This list, while not exhaustive, highlights some of the contributory mechanisms to diastolic dysfunction of the left ventricle.

Thus, in selected patients, acute pulmonary oedema can be due to exacerbation of diastolic dysfunction by hypertension and not due to transient systolic dysfunction or mitral regurgitation.

The key point, therefore, is that in a patient who has had heart failure, normal systolic function on an echocardiogram does not refute the diagnosis. In the setting of normal or near normal ventricular function, heart failure may have arisen from diastolic dysfunction of the left ventricle or reversible systolic dysfunction.

Who gets diastolic heart failure?

The reported prevalence of pure diastolic heart failure varies widely, accounting for between 13 and 74% of all hospital admissions for congestive cardiac failure.[5] There is an apparent higher incidence in the elderly, accounting for up to 50% of all cases of congestive cardiac failure admissions in adults over 65 years of age.[6] Women have a slightly higher incidence of diastolic heart failure than systolic heart failure, whereas men have proportionately more systolic dysfunction heart failure at all ages.[7,8] Diastolic heart failure is more common than systolic heart failure in the Chinese population;[9] this may be related to the older age at presentation and the higher prevalence of hypertension in this community.

One of the problems limiting the precise delineation of the aetiology of congestive cardiac failure is the potential coexistence of systolic and diastolic dysfunction in an individual patient.

What is the mechanism?

The normal cardiac cycle and diastole

The normal cardiac cycle, most simply, is LV contraction (systole) and LV relaxation and filling (diastole).

The isovolumic relaxation phase occurs between closure of the aortic valve and opening of the mitral valve. Early filling of the left ventricle occurs just after mitral valve opening, and active diastolic relaxation contributes to this phase. Atrial systole provides a boost of pressure gradient and causes renewed late filling.

Mechanism of diastolic dysfunction

Anything that interferes with relaxation or filling of the left ventricle can impair diastolic function.

Multiple factors contribute to diastolic dysfunction, including valvular heart disease, myocardial ischaemia, fibrosis, hypertrophy and restriction, and pericardial constriction (Table 2). For example, when haemodynamically challenged with exercise, tachycardia or excess fluid load, patients with hypertension – especially those with LV hypertrophy (LVH) – are unable to increase their end-diastolic volume appropriately because of decreased LV relaxation and compliance. Hence, ventricular and atrial pressures increase and pulmonary oedema develops.

At a cellular level, hypertrophic myocytes have abnormal Ca^{2+} cycles, including prolonged calcium transients and hence impaired relaxation. This may be induced by local activity of various neurohormonal agents, including angiotensin-II. Other potential mediators contributing to LV dysfunction include endothelin, atrial natriuretic peptide, brain natriuretic peptide, and aldosterone.[10] This has been reviewed recently in detail elsewhere.[11]

Brain natriuretic peptide assays have been developed to assess both systolic and diastolic dysfunction heart failure. Levels of these peptides are elevated in congestive cardiac failure and seem to correlate well with LV end-diastolic

pressure (LVEDP);[12] however, further studies are required to validate these observations before they can be applied to routine clinical practice.[13] There is some evidence that brain natriuretic peptides may also prove useful in titrating treatment for congestive cardiac failure.[14] Whether these peptides will discriminate between diastolic and systolic heart failure is currently unclear.

How do you diagnose it?

Symptoms of congestive cardiac failure with preserved systolic LV function indicate a likely diagnosis of diastolic heart failure. A definite diagnosis of congestive cardiac failure must first be made (see Table 1). In patients with systolic dysfunction, looking for diastolic dysfunction does not alter management as the treatment of systolic dysfunction takes priority. Diastolic dysfunction should be sought when there is clear progressive or recurrent heart failure with normal or only mildly abnormal systolic function.

- **Bedside clues** that may indicate possible diastolic dysfunction include pulmonary oedema in a patient with long-standing hypertension (especially if he or she is elderly) with clinical and electrocardiographic evidence of LVH.
- **Echocardiography** remains the primary tool for demonstrating diastolic dysfunction and its underlying aetiology. Traditional echocardiographic assessment of diastolic function includes the use of Doppler recordings of:
  - flow velocity across the mitral valve, representing transmitral pressure gradient
  - pulmonary venous flow velocity, representing left atrial filling.
- **Cardiac catheterisation**, although the definitive method of defining diastolic function using pressure and volume measurements, is rarely indicated or performed for the diagnosis of diastolic heart failure.
- **Radionucleotide scintigraphy** (gated blood pool scanning) has been used to analyse parameters, such as peak filling rate, atrial filling fraction and end-diastolic response to exercise,[15] but is used infrequently to prove diastolic dysfunction.

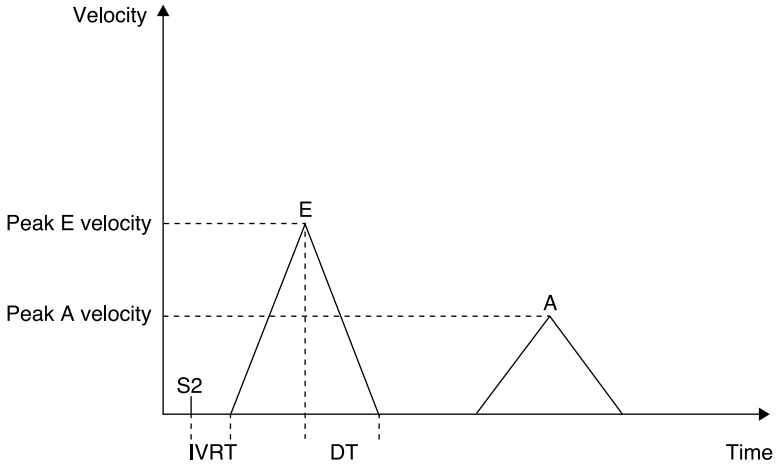
What to look for on an echo report

When examining an echocardiographic report for a patient in whom diastolic dysfunction is suspected, look for the following:

- normal or near normal LV systolic function: an ejection fraction of at least 45%

Assessing diastolic dysfunction by echocardiography

The main technique used to assess diastolic dysfunction is transthoracic echocardiography using Doppler recordings of flow velocities across the mitral valve (representing transmitral pressure gradient) and in the pulmonary veins (representing left atrial filling). Four distinct early filling/late filling ratio patterns are recognised (see below).



Echodoppler recording of mitral inflow velocity.

Reference values to assess and classify diastolic filling

Doppler measures	Normal	Impaired relaxation	Pseudo-normalisation	Restrictive filling
E/A ratio	1–2	<1	1–2	>1.5
DT	160–240 ms	>240 ms	160–200 ms	<160 ms
IVRT	70–90 ms	>90 ms	<90 ms	<70 ms
Pulmonary venous flow	PVs≥PVd	PVs>>PVd	PVs~PVd	PVs<<PVd

Abbreviations and explanations. S2 = second heart sound. E velocity = peak mitral flow velocity of early rapid ventricular filling. A velocity = peak mitral flow velocity of late ventricular filling (atrial systolic). DT = deceleration time – i.e. the interval from peak of E velocity to its extrapolation to the baseline. IVRT = isovolumic relaxation time – i.e. the interval from closure of aortic valve to opening of mitral valve (this parallels deceleration time). E/A = early filling/late filling of the left ventricle. PVs = pulmonary venous flow velocity in systole. PVd = pulmonary venous flow velocity in diastole.

- LV diastolic dysfunction: indicated by distinct patterns on Doppler recordings of mitral inflow velocity and pulmonary venous velocity
- associated conditions:
  - valvular anatomy and function for signs of aortic stenosis, mitral stenosis
  - left atrial size for signs of impaired LV filling (enlarged left atrium)
  - LV wall thickness for LVH in hypertension, asymmetric hypertrophy in hypertrophic obstructive cardiomyopathy
  - LV muscle texture for 'scintillation' in amyloidosis
  - pericardium for thickening and constriction.

As described in the box on page 25, there are four distinct early filling/late filling (E/A) ratio patterns:

- normal
- impaired relaxation
- pseudonormalisation
- restrictive.

These patterns may evolve in any single patient from one to the other with changes in loading condition, treatment and disease progression;[16] this complicates their interpretation. In most disease states the initial diastolic abnormality is

How to treat diastolic heart failure

- Treat the acute episode: reduce pulmonary congestion with salt and fluid restriction, diuretics or nitrates
- Treat any acute precipitants – e.g. arrhythmias, infection, ischaemia, uncontrolled hypertension
- Treat the underlying cause:
  - lower blood pressure to 130/80 mmHg or less
  - reduce heart rate (to increase diastolic filling time) using beta blockers, or digoxin [Lanoxin] and/or verapamil if the patient has atrial fibrillation
  - maintain atrio-ventricular (A-V) synchrony (to aid late diastolic filling by atrial systole) by sequential A-V pacing or cardioversion if patient has atrial fibrillation
  - treat any underlying ischaemia using beta blockers and/or coronary revascularisation, etc.
  - promote regression of left ventricular hypertrophy (e.g. by ACE inhibition)
  - correct valvular heart disease (e.g. aortic valve replacement for aortic stenosis)
- Optimise physical activity and ensure compliance with diet and medication

impaired relaxation where the early filling/late filling ratio diminishes (to less than 1). As the dysfunction progresses, the left atrial pressure increases and so does the early filling/late filling ratio, which returns to greater than 1 (pseudonormalisation). This stage can be distinguished from the normal by parameters such as deceleration time and isovolumic relaxation time. With further increase in left atrial pressure and reduction in LV compliance, diastolic filling becomes restrictive.

What is the prognosis?

Data are lacking on the prognosis of patients with isolated diastolic heart failure. Generally, patients with preserved systolic function have a more favourable outlook than those with poor systolic function.[17] A restrictive filling pattern on echodoppler suggests a worse prognosis and must be aggressively evaluated for reversibility with treatment.[18,19] Diastolic dysfunction in some patients represents an irreversible or progressive process – for example, fibrosis or infiltration with amyloid – and thus a poor prognosis.

How do you treat it?

As there is no consensus on the ideal treatment strategy for isolated diastolic heart failure, management has been largely empirical. As with systolic heart failure, the acute episode must be treated and potentially reversible processes contributing to impaired diastolic function addressed.

Major distinctions in the treatment of diastolic heart failure from that of systolic heart failure include the avoidance of inotropes and the treatment of conditions that worsen cardiac filling (such as tachycardia, LVH). The box on page 27 summarises the treatment of diastolic heart failure.

As discussed below, several classes of pharmacological agents may be useful in the treatment of diastolic heart failure, and their use must be tailored to the individual patient.

Important lifestyle measures, such as restricted dietary salt intake, careful fluid management and optimising physical exercise, need to be addressed by the GP as they contribute to clinical outcomes and quality of life. Patients with chronic heart failure should be advised to be vaccinated against influenza and pneumococcal infections. Alcohol intake should be nil, but not exceed 20 g/day. The GP also has a crucial role in ensuring patient compliance with these measures and medication.

Treating the acute episode

- **Diuretics and nitrates** should be used judiciously to reduce pulmonary congestion without excessively reducing preload. Reducing preload runs the risk of reducing cardiac output in these patients. The dose of both diuretics and nitrates must be carefully monitored against the development of hypotension.
- **Inotropes** have almost no role in the treatment of pure diastolic dysfunction except when there is associated systolic dysfunction. Generally, normal systolic function does not require inotropic support.
- **Digoxin** (Lanoxin) may augment contractility, increasing LV filling pressures, and is not indicated for

patients in sinus rhythm with preserved systolic function. However, it is indicated to control ventricular rate in patients with rapid atrial fibrillation.

Other treatments

Beta blockers

Beta blockade (for example, with metoprolol or carvedilol [Dilatrend]) is now an established treatment strategy for patients with heart failure and is known to improve survival; however, the growing body of evidence for this is predominantly in patients with established systolic dysfunction. The beneficial effect of these agents on diastolic dysfunction may indirectly follow reduction of heart rate, blood pressure and myocardial oxygen demand, and/or regression of LVH, rather than having a direct action on myocardial relaxation. There are overwhelming data supporting the use of beta blockers in congestive cardiac failure.[20]

ACE inhibitors

ACE inhibitors are important prognostically for the management of patients with LVH.[21] They are more effective in causing regression of LVH than beta blockers, calcium channel blockers or diuretics.[22] ACE inhibition may produce beneficial effects on diastolic function via direct myocardial action, in addition to lowering blood pressure and reducing LV mass.

Calcium channel blockers

Calcium channel blockers (for example, verapamil and diltiazem) reduce heart rate, blood pressure, and myocardial oxygen demand and promote regression of LVH. Theoretically, calcium channel blockers should reduce intracellular calcium load and hence improve diastolic function. There is considerable variation, however, in the clinical response to these drugs, and there is no definite evidence of the prognostic benefit of calcium channel blockers for congestive cardiac failure.

Spironolactone

Spironolactone (Aldactone, Spiractin) has been shown to reduce mortality in patients with systolic dysfunction heart failure,[23] but there are no studies to date evaluating its effect in diastolic heart failure.

Surgery

Surgical management of diastolic heart failure includes valve replacement for aortic stenosis, pericardiectomy for chronic constrictive pericarditis and pericardial aspiration for cardiac tamponade.

What follow up is needed?

The follow up of patients with diastolic heart failure is the same as that for systolic heart failure; particular attention should be paid to underlying conditions, such as rigorous control of hypertension and prevention of LVH. Ongoing assessment of functional capacity is important in the management of patients with heart failure and should include physical capacity, emotional status, social function and cognitive abilities.

Conclusion

Although the diagnosis of diastolic heart failure is difficult to prove, it is an established clinical entity and should be considered in patients with definite congestive cardiac failure in the presence of normal, or almost normal, systolic function of the left ventricle. With our ageing population, diastolic heart failure is likely to remain a significant public health issue. MT

A list of references is available on request to the editorial office.

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References

1. European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. Eur Heart J 1998; 19: 990-1003.
2. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved left ventricular function suffer from "Diastolic heart failure" or from misdiagnosis? A prospective descriptive study. BMJ 2000; 321: 215-218.
3. Guidelines for the evaluation and management of heart failure. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). J Am Coll Cardiol 1995; 26: 1376-1398.
4. Gandhi SK, Powers JC, Nomier AM, Fowle K, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med 2001; 344:17-22.
5. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure. J Am Coll Cardiol 1995; 26: 1565-1574.
6. Rich MW. Epidemiology, pathophysiology, and etiology of congestive heart failure in older adults. J Am Geriatr Soc 1997; 45: 968-974.
7. Diller PM, Smucker DR, David B, Graham RJ. Congestive heart failure due to diastolic or systolic dysfunction. Frequency and patient characteristics in an ambulatory setting. Arch Fam Med 1999; 8: 414-420.
8. Devereux RB, Roman MJ, Liu JE, et al. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. Am J Cardiol 2000; 86: 1090-1096.
9. Yip GW, Ho PP, Woo KS, Sanderson JE. Comparison of frequencies of left ventricular systolic and diastolic heart failure in Chinese living in Hong Kong. Am J Cardiol 1999; 84: 563-567.
10. Kessler KM. Heart failure with normal systolic function. Arch Intern Med 1988; 148: 2109-2111.
11. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 1999; 341(8): 577-585.
12. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998; 135: 825-832.
13. Bettencourt P, Ferreira A, Dias P, Castro A, Martins L, Cerqueira-Gomes M. Evaluation of brain natriuretic peptide in the diagnosis of heart failure. Cardiology 2000; 93: 19-25.
14. Dries DL, Stevenson LW. Brain natriuretic peptide as bridge to therapy for heart failure. Lancet 2000; 355: 1112-1113.
15. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol 1991; 17: 1065-1072.
16. Oh JK, Seward JB, Tajik AJ. The Echo Manual. 2nd ed, Philadelphia: Lippincott-Raven, 1999.
17. Cohn JH, Johnson G. Veterans administration cooperative study group. Heart failure with normal ejection fraction: the V-HEFT study. Circulation 1990; 81(Suppl 3): 48-53.
18. Pinamonti B, Zecchin M, Di Lenarda A, Gregori D, Sinagra G, Camerini F. Persistence of restrictive left ventricular filling pattern in dilated cardiomyopathy: an ominous prognostic sign. J Am Coll Cardiol 1997; 29: 604-612.
19. Lee DC, Oh JK, Osborn SL, Mahoney DW, Seward JB [abstract]. Repeat evaluation of diastolic filling pattern after treatment of congestive heart failure in patients with restrictive diastolic filling: implication for long term prognosis. J Am Soc Echocardiogr 1997; 10: 431.
20. Doughty RN, Rodgers A, Sharpe N, MacMahon S. Effects of beta blocker therapy on mortality in patients with heart failure: a systematic overview of randomized controlled trials. Eur Heart J 1998; 8: 560-565.
21. Garg R, Yusuf S. Overview of randomized trials of ACE inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995; 273: 1450-1456.
22. Dahlof B, Pennert K, Hansson L. Reversal of left ventricular hypertrophy in hypertensive patients. A meta-analysis of 109 treatment studies. Am J Hypertension 1992; 5: 95-110.
23. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999; 341: 709-717.