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Clinical Practice 2008: Heart Failure With Preserved Systolic Function

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Diagnosis and Treatment of Heart Failure with Preserved Ejection Fraction

Much attention has been given to heart failure (HF) with reduced ejection fraction (or systolic heart failure), and clinical practice guidelines have been developed for the treatment of this type of HF. However, less evidence has been available for the pathophysiology or treatment of HF with preserved ejection fraction (or diastolic heart failure). Enhanced understanding of diastolic HF is crucial, because it is more common than systolic HF and its prevalence is increasing. A special session provided an overview of the diagnosis, pathophysiology, and treatment of diastolic HF and compared its characteristics with those of systolic HF.

Diagnosis

"Observational studies have given a remarkably consistent view of the [diastolic HF] syndrome," said Margaret Redfield, MD, Mayo Clinic, Rochester, MN. In such studies, said Dr. Redfield, patients with diastolic HF (compared with patients who have systolic HF) have been older, more often female, less likely to have coronary artery disease, and very likely to have hypertension. Subsequent randomized clinical trials have presented conflicting data, with the results of some trials confirming these characteristics and others providing a slightly different clinical presentation.

Dr. Redfield noted that an updated consensus statement from the European Society of Cardiology and the Echocardiography Associations of the European Society of Cardiology established diagnostic criteria for diastolic HF whose presence should be based on assessment of left ventricular geometry, atrial size, diastolic function on Doppler imaging, and brain natriuretic peptide (BNP) testing, with invasive hemodynamic measurements if necessary [Paulus et al. *Eur Heart* 2007]. She recommended that a "multimarker strategy" be followed when evaluating a patient with symptoms that are suggestive of HF and an ejection fraction of ≥50%. The more "yes" answers to the following questions, she said, the greater the probability that the patient has diastolic HF.

- Is the pulmonary artery systolic pressure elevated?
- Is the spectral tissue Doppler echocardiography E/E' ratio elevated?
- Is the left atrium enlarged?
- Is there left ventricular hypertrophy or concentric remodeling?
- Is the BNP level elevated?
- Do the symptoms correlate with onset atrial fibrillation?
- Is there a response to diuretics?
- Are the findings on chest x-ray and physical examination consistent with HF?

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Pathophysiology

Michael Zile, MD, Medical University of South Carolina, Charleston, SC, noted the prevalence of some of the features that were discussed by Dr. Redfield in his discussion of the pathophysiology of diastolic HF. For example, he said that increased atrial size has been found in 64% to 71% of patients with diastolic HF, and left ventricular hypertrophy or concentric remodeling has been found in 40% to 50% of such patients [Persson et al. *J Am Coll Cardio* 2007; Massie et al. *N Engl J Med* 2008]. Dr. Zile also outlined some significant differences between the 2 types of HF in terms of left ventricular structure and function (Table 1).

Table 1. Comparison of Structure and Left Ventricular Function Between Systolic and Diastolic HF.

	Diastolic HF	Systolic HF
Remodeling of left ventricle	Concentric	Eccentric
Left ventricular cardiomyocytes	Increase in diameter	Significant increase in length
Estracellular matrix fibrillar collagen	Significant accumulation	Significant disruption

"There are significant differences in diastolic function between patients with systolic HF and diastolic HF," added Dr. Zile. Randomized clinical trials have shown that diastolic dysfunction (grade 1-3) is evident in 67% to 81% of patients with diastolic HF [Persson et al. *J Am Coll Cardiol* 2007; Massie et al. *N Engl J Med* 2008]. Dr. Zile added that left ventricular distensibility is different at the left ventricular chamber, myocardial, and cardiomyocyte levels; while distensibility is increased or unchanged in patients with systolic HF, it is substantially decreased in patients with diastolic HF.

Treatment

In discussing current treatment options, Philip Poole-Wilson, MD, Imperial College, London, UK, pointed out that the general principles for the treatment of diastolic HF are the same as those for systolic HF and that the same drugs are used. He noted that randomized controlled trials have shown that digitalis, perindopril, and candesartan have not shown benefit in terms of mortality, HF-related hospitalization, and quality-of-life measures (eg, 6-minute walk test) [Ahmed et al. *Circulation* 2006; Cleland et al. *Eur Heart J* 2006; Yusuf et al. *Lancet* 2003]. One trial, for which Dr. Poole-Wilson was an investigator, showed that nebivolol, a beta-blocker that has vasodilating properties, led to lower all-cause mortality and cardiovascular hospitalizations [Flather et al. *Eur Heart J* 2005].

Dr. Poole-Wilson said that the overall treatment of patients with diastolic HF should focus on maintaining atrial contraction (by preventing and treating atrial fibrillation), controlling hypertension, addressing ischemia, and preventing tachycardia and hypertrophy. David Feldman, MD, PhD, Ohio State University, Columbus, OH, agreed with this treatment approach and noted some specific strategies (Table 2). Dr. Feldman also discussed future treatments, first describing the cellular mechanisms that contribute to the progression of HF. He explained that HF is defined as an inability of the heart to support the metabolic and physiological needs of the body. This syndrome often is related to an initial phase of cardiac injury followed by a chronic, progressive, and generally accelerating progression of disease, culminating in a patient who presents for medical care. A hallmark feature of HF progression in humans is the time-dependent adaptation of myocardium, leading to changes in cardiac myocyte performance or survival, and changes in myocardial tissue composition. For example, ventricular chamber dilation, myocyte hypertrophy, and interstitial fibrosis all are well-recognized features of cardiac adaptations in HF. Future ventricular and cell biology targets include receptor-mediated signaling, sarcoplasmic reticulum manipulation, myofilament alterations, and agents that alter the extracellular matrix and attenuate fibrosis, as well as new stem cell-based therapies.

Table 2. Potential Treatment Strategies for Patients With HF and Preserved Systolic Function.

- Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker and beta-blocker*
- Exercise
- Consideration of aldosterone antagonist for patients with continued symptoms
- Minimal dose of a diuretic
- Secondary prevention with aspirin
- Statin therapy to target a low-density lipoprotein level of approximately 70-80 mg/dL
- Treatment to achiev to blood pressure target of 110/70 mm Hg
- Treatment of diabetes to a target hemoglobin A1c of ≤6.5%
- Evaluation of obstructive sleep apnea
- Normalize body weight and improve diet (eg, reduce sodium intake)

*Consistent with the American College of Cardiology/American Heart Association guidelines for the management of heart failure (stage B and C)

Hunt et al. *Circulation.* 2005.