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Management of asymptomatic left ventricular dysfunction

ABSTRACT

Asymptomatic left ventricular dysfunction should be treated as an early stage on the continuum that is chronic heart failure. The author presents the clinical trial data on which current management with angiotensin-converting enzyme inhibitors and beta-blockers is based. Issues surrounding screening are also discussed.

KEY POINTS

The SOLVD, SAVE, and other trials have firmly established the value of giving angiotensin-converting enzyme (ACE) inhibitors to patients with asymptomatic left ventricular dysfunction.

The value of beta-blockers in combination with ACE inhibitors in this population is less well established, but these drugs are probably beneficial.

Any screening strategy for asymptomatic left ventricular dysfunction must focus on groups at high risk: the elderly, those with ischemic heart disease, hypertension, diabetes, electrocardiographic abnormalities, morbid obesity, a family member with dilated cardiomyopathy, or exposure to myocardial toxins. Whether screening can be cost-effective remains to be seen.

ASYMPTOMATIC LEFT VENTRICULAR (LV) dysfunction is an early stage on the continuum of chronic heart failure, and we should manage it as such.

We now know that the neurohormonal responses and other processes that contribute to LV dysfunction can progress without causing clinical symptoms. Drug treatments that target these neurohormonal abnormalities can slow or prevent progression of heart failure not only in patients with moderate or severe symptoms, but also in those with LV dysfunction and few or no symptoms.[1–4] The possibility that we can delay or prevent the symptoms and chronic disability of heart failure raises the question of how best to identify persons with asymptomatic LV dysfunction and treat them before the onset of symptoms. This would reduce the incidence of symptomatic heart failure and its associated morbidity and mortality.

In this article, I discuss the factors underlying asymptomatic LV dysfunction, the relationship of asymptomatic LV dysfunction to the overall syndrome of chronic heart failure, and therapy with angiotensin-converting enzyme (ACE) inhibitors and beta-blockers. I outline strategies for prevention and address the issue of screening for asymptomatic LV dysfunction.

LV REMODELING AND HEART FAILURE: A CONTINUUM

Heart failure is a continuum, and asymptomatic LV dysfunction is an early stage on that continuum. The process starts with an initial injury to the myocardium, brought on by any one or a combination of the following:

- A sustained stimulus for myocyte hypertrophy, such as hypertension or valvular disease
- An intrinsic abnormality of cardiac function, such as cardiomyopathy
- Coronary artery disease.[5]

Myocyte injury produces changes in loading conditions, which in turn lead to detrimental cardiac remodeling: the LV chamber dilates, hypertrophies, and becomes more spherical.[2,5] A resultant decrease in peripheral organ blood flow triggers a variety of humoral, neurohormonal, and inflammatory responses. The initial systemic response is to compensate for the deficiency in the heart's pumping ability, but eventually the response only precipitates further cardiac remodeling.

Clues for intervention

Together, these processes represent an insidious stage in which progressive enlargement of the left ventricle is associated with a time-dependent deterioration in LV function. Most patients who manifest the clinical syndrome of chronic heart failure pass through this stage without symptoms. Objective measurements reveal impaired contractility without overt heart failure.

Heart failure can have an insidious onset

Several important clinical trials, discussed below, demonstrate the benefits of early medical intervention with ACE inhibitors and beta-blockers.

TRIALS OF ACE INHIBITORS IN ASYMPTOMATIC LV DYSFUNCTION

The results from two landmark studies[3,4] published in 1992 form the basis for current management of asymptomatic LV dysfunction.

The SOLVD Prevention trial

To test whether identifying patients with asymptomatic LV dysfunction and treating them with the ACE inhibitor enalapril would reduce morbidity and mortality,[5] the prevention arm of the Studies of Left Ventricular Function (SOLVD) trial enrolled only patients with asymptomatic or minimally symptomatic LV dysfunction.[3] (Another arm of the SOLVD trial looked at treatment of symptomatic heart failure.)

Patients had little or no limitation in exercise tolerance attributed to dyspnea or fatigue. They were not receiving digoxin, diuretics, or vasodilators, and no cause of LV dysfunction was specified. A total of 4,228 patients with LV ejection fractions of 35% or below were randomized to receive either enalapril titrated to a target dose of 10 mg twice a day or placebo.

At an average follow-up of 3.5 years, 20.7% of patients in the enalapril group developed symptomatic congestive heart failure compared with 30.2% of placebo-treated patients—a 37% reduction ($P \leq .0001$). The combined end point of death or hospitalization due to heart failure occurred in 20.6% of enalapril-treated patients vs 24.5% of placebo-treated patients, a 16% relative risk reduction ($P \leq .001$). There was a trend toward mortality reduction with enalapril treatment (14.1% vs 12.6%; $P = .12$). Notably, 83% of patients in the SOLVD Prevention trial had an ischemic cause of LV dysfunction, which underscores the importance of preventive control of coronary artery disease.

The two arms of the SOLVD trial also showed that clinical status was of prognostic importance. In the placebo group, patients with clinical symptoms of heart failure had a 40% mortality rate over 41 months, compared with 16% in patients without symptoms.

Another important finding was that, once clinical status was determined, the likelihood of death for those who developed symptoms was twice as high as for those who remained free of symptoms, regardless of the treatment.

These observations underscore the importance of identifying patients at an asymptomatic stage of LV dysfunction, when treatment that can delay or prevent the onset of symptomatic heart failure can be instituted.

The SAVE trial

The Survival and Ventricular Enlargement (SAVE) trial[4] was the first direct attempt at proving whether patients with asymptomatic LV dysfunction following a recent myocardial infarction (MI) improve clinically with treatment.[4] Pfeffer and colleagues[6] had previously shown that ACE inhibitors could attenuate LV remodeling after experimental MI in an animal model.

The SAVE trial enrolled 2,231 patients

who had suffered an MI from 3 to 16 days earlier. All had LV ejection fractions of 40% or less and were eligible for the study only if they had not experienced heart failure symptoms. They were randomized to receive the ACE inhibitor captopril or placebo. The captopril dosage was titrated to 50 mg three times a day. The average follow-up was 3.5 years.

The major findings from this study were that treatment with captopril significantly reduced all-cause mortality (20% vs 25% in the placebo group; 20% relative risk reduction; $P = .019$) and the risk of developing symptomatic congestive heart failure requiring hospitalization (14% vs 17% in the placebo group; 18% relative risk reduction; $P = .019$). Consistent with the SOLVD data, patients developing symptomatic heart failure were three to six times more likely to suffer a fatal cardiac event.

Prevention of LV remodeling. An echocardiographic substudy of the SAVE cohort found that attenuation of LV enlargement (ie, prevention of remodeling) reduced the incidence of symptomatic heart failure and death.[7] Regardless of treatment assignment, patients who suffered a cardiovascular event (defined as cardiovascular death, heart failure requiring either hospitalization or open-label ACE inhibitor therapy, or recurrent infarction) had a more than threefold greater increase in LV area from baseline to 1 year than patients who suffered no event.[7] Furthermore, a subgroup of patients with progressive LV enlargement despite captopril treatment had a cardiovascular event rate similar to that of placebo-treated patients. Therefore, failure to prevent LV remodeling was a strong predictor of adverse outcome.

The AIRE and TRACE studies

The results from the SAVE trial are consistent with findings from two other studies of post-MI patients, in which a substantial number had asymptomatic or minimally symptomatic LV dysfunction.

The Acute Infarction Ramipril Efficacy (AIRE) trial[8] and the Trandolapril Cardiac Evaluation (TRACE) study[9] evaluated the efficacy of the ACE inhibitors ramipril and trandolapril, respectively, in almost 4,000 patients with LV dysfunction after MI. In both studies, treatment with the ACE inhibitor significantly decreased all-cause mortality and the risk of severe or refractory heart failure.

BETA-BLOCKERS IN ASYMPTOMATIC LV DYSFUNCTION

Beta-blockers are proven effective in heart failure patients with mild to moderate symptoms. For patients with asymptomatic LV dysfunction, studies have shown that using beta-blockers together with ACE inhibitors improves survival to a greater extent than ACE inhibitors alone.

Mechanisms of action

Beta-blockers have several properties that may account for their beneficial effect:

- They block the sympathetic nervous system. Plasma norepinephrine levels are elevated in many patients with asymptomatic LV dysfunction and may be of prognostic importance.[10] That these agents antagonize the adverse effects of catecholamines would seem to be consistent with the overall benefits of neurohormonal antagonism in heart failure.
- They are antiarrhythmic and therefore may prevent sudden death.[11]
- They limit heart rate and therefore prevent ischemia.
- They can reverse cardiac remodeling.[12]

For all these reasons, beta-blockers are the standard of care for acute ischemic syndromes.

Neurohormonal abnormalities may precede the onset of symptoms

Evidence for combined therapy

Exner et al[13] performed a post hoc analysis of the prevention arm of the SOLVD trial to determine the effect of beta-blockers combined with ACE inhibitors on mortality in asymptomatic LV dysfunction. In all, 513 of the 1,015 patients taking beta-blockers were randomized to receive enalapril. The lowest mortality rates from both arrhythmias and pump failure were in patients taking both medications. The investigators concluded that the use of beta-blockers with ACE inhibitors was associated with a synergistic reduction in mortality.

However, a major limitation of this study is that it was retrospective. Data from prospective evaluations of beta-blockade in asymptomatic LV dysfunction are sparse.

TABLE 1

Risk factors for LV dysfunction: Potential targets for screening

- Elderly
- Ischemic heart disease
- Hypertension
- Diabetes
- Electrocardiographic abnormality
  - Left ventricular hypertrophy
  - Q waves
  - Bundle branch block
- Morbid obesity
- Family member with dilated cardiomyopathy
- Exposure to myocardial toxins (ie, anthracyclines)

Routine use of beta-blockers needs further study

The current recommendation is to start ACE inhibitor therapy in all patients with asymptomatic LV dysfunction (LV ejection fraction 35% to 40%) regardless of the cause.[14] The routine use of beta-blockers in this population requires further study, but data are emerging in support of their use in combination with an ACE inhibitor in some patients, particularly those with ischemic heart disease.[15] Beta-blocker therapy is clearly indicated after an MI.

Most heart failure is due to coronary artery disease

IS SCREENING FOR ASYMPTOMATIC LV DYSFUNCTION FEASIBLE?

By detecting heart failure at an early, asymptomatic stage and starting therapy to delay or prevent symptoms (by preventing LV remodeling), we can significantly reduce heart failure morbidity and mortality. But for this to occur on a large scale, we need to detect *asymptomatic* LV dysfunction in the general population at risk, which is not an easy task. Therefore, the issue of screening faces important questions about feasibility.

Experience with the development of successful screening programs for diseases such as cancer and hypertension has taught us that a screening method must meet several well-established criteria of effectiveness. Asymptomatic LV dysfunction meets most of these criteria:[16]

- The condition should be a precursor of an important health problem
- The condition must have a recognizable latent or early asymptomatic stage
- There must be an accepted treatment that reduces disability, death, or both
- There must be a valid and acceptable test for the condition
- Screening should be cost-effective.

Of all these criteria, the cost-effectiveness remains the one area of uncertainty.

Heart failure is an important public health problem

Chronic heart failure is extremely common in the general population, and its prevalence is on the rise. The prevalence is projected to nearly double to 5.7 million cases by the year 2030.[1] The increasing prevalence of heart failure is likely due to multiple factors, including the increasing age of the population, improved treatment of coronary artery disease (the major precursor of LV dysfunction), and perhaps also a greater public awareness of heart failure. Chronic heart failure now accounts for approximately 5% of all adult medical and acute geriatric admissions, or 1% to 2% of all health care expenditures.[16]

Risk factors that may signal which people to screen

A better understanding of the natural history of heart failure improves our chances of identifying which populations to screen. High-risk groups would need to be identified, such as patients with a history of coronary artery disease, MI, angina, hypertension, or diabetes (TABLE 1). Any one of these conditions in the elderly would further increase risk.

Coronary artery disease. In the United States, coronary artery disease is a frequent precursor to LV dysfunction. The Framingham Heart Study demonstrated that the risk of developing symptomatic heart failure was increased 10-fold in survivors of MI compared with the normal population. Those with angina but no prior infarct exhibited an intermediate risk (FIGURE 1).[17] In the SOLVD Prevention trial, which enrolled patients with LV dysfunction regardless of etiology, 83% of patients had ischemic heart disease.[3] The

combination of hypertension and ischemic heart disease appears to be a particularly powerful predictor of LV dysfunction.[18]

Identification of patients at risk for chronic heart failure is confounded by the observation that as many as one third of MIs are clinically silent. This is particularly true for certain higher-risk groups that may be targeted for screening, such as the elderly and those with diabetes.[18]

Left ventricular enlargement. Echocardiographic studies have identified other populations at higher risk of progression to LV dysfunction in the absence of identifiable MI.[19] LV enlargement with otherwise normal systolic function has been shown to be a risk factor for subsequent heart failure over long-term follow-up (11 years), even in patients with no history of MI. Also, nearly one third of asymptomatic relatives of patients with idiopathic dilated cardiomyopathy may have echocardiographic abnormalities, and 27% may develop overt heart failure.[20]

What is the best screening test for asymptomatic LV dysfunction?

Echocardiography. For screening to be successful, we must be able to evaluate large populations in a cost-effective manner. Echocardiography is a valuable tool for cardiac evaluation and will play a major role in any screening process. It has been shown to be useful for both diagnosis and prognosis. In a retrospective analysis of the Rochester Epidemiologic Project,[21] patients who underwent echocardiography tended to receive ACE inhibitors more often and therefore had a higher survival rate compared with those who did not undergo echocardiography.[21]

Still, echocardiography is too expensive to be done indiscriminately, and its use would have to be confined to high-risk populations, such as the elderly. Morgan et al[22] found that approximately 1 in 10 patients ages 75 to 84 years who underwent echocardiography had significant LV systolic dysfunction.[22] In most cases, the clinical history and examination failed to identify this. Clearly, reliance on the clinical evaluation alone would result in a failure to identify many patients who would benefit from treatment.

Framingham data: Coronary artery disease increases risk of heart failure

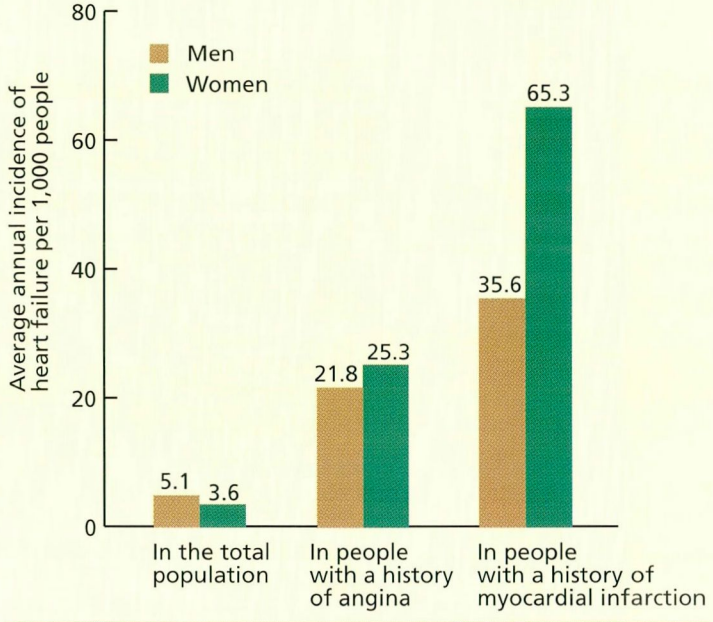

FIGURE 1. Age-adjusted risk of developing congestive heart failure according to prior coronary heart disease status in the Framingham study (18-year follow-up in men and women 45 to 74 years old).

ADAPTED FROM KANNEL WB, SAVAGE D, CASTELLI WP. CARDIAC FAILURE IN THE FRAMINGHAM STUDY: TWENTY-YEAR FOLLOW-UP. IN: BRAUNWALD E, MOCK MB, WATSON JT, EDITORS. CONGESTIVE HEART FAILURE: CURRENT RESEARCH AND CLINICAL APPLICATIONS. NEW YORK: GRUNE & STRATTON, 1982.

B-type natriuretic peptide (BNP) levels in plasma are being investigated as a screening test for asymptomatic LV dysfunction.[23–25] BNP levels have been used for the screening, diagnosis, clinical management, and prognostic assessment of patients with chronic heart failure. BNP measurements may be useful for targeting patients with suspected LV dysfunction who may require further diagnostic evaluation. The US Food and Drug Administration recently approved the Triage BNP test (Biosite Diagnostics, Inc), a rapid, point-of-care immunoassay that measures levels of BNP from approximately six drops of whole blood or plasma. The sensitivity and cost-effectiveness of this method for detecting mild LV dysfunction—and thus, its usefulness as a screening tool—require further evaluation.

Plasma norepinephrine levels are of prognostic importance and are known to be

TABLE 2

Preventive strategies for asymptomatic LV dysfunction

Primary prevention
Attenuate cardiovascular risk factors
- Hypertension control
- Lipid management
- Abstinence from cigarette smoking
- Exercise and weight loss
- ACE inhibitor therapy for atherosclerotic heart disease, hypertension, diabetes (based on HOPE trial results)

Secondary prevention
Screening to identify asymptomatic LV dysfunction

Forestall onset of symptoms by preventing LV remodeling
- ACE inhibitors
- Beta-blockers
- Management of postmyocardial infarction patient with both an ACE inhibitors and a beta-blocker

elevated in asymptomatic patients with LV dysfunction but are not a useful screening tool because of the difficulty in performing this measurement reliably in clinical practice.[10]

The HOPE trial: Perhaps all patients with coronary disease should receive ACE inhibitors

Current recommendations for screening

A successful screening program for asymptomatic LV dysfunction would target higher-risk populations (as listed in TABLE 1) for echocardiography, which is currently the diagnostic gold standard. Perhaps the measurement of BNP in high-risk populations can eventually be used to better direct echocardiography and therefore to improve its cost-effectiveness in screening for asymptomatic LV dysfunction.

PREVENTING LV DYSFUNCTION

Preventing the onset of disease (primary prevention) is the best way to avert the devastating morbidity and mortality of chronic heart failure (TABLE 2). Preventive measures include control of hypertension, lipid management, abstinence from cigarette smoking, avoidance of obesity, and adoption of a more active lifestyle.

Hypertension control is key

The importance of aggressively managing hypertension, particularly systolic hypertension, should be emphasized, because in middle age and old age systolic blood pressure appears closely related to the development of heart failure. At least two large studies[26,27] report that the treatment of hypertension dramatically reduces the incidence of heart failure and other cardiovascular events.

Unfortunately, although we now have numerous options for treating hypertension, many hypertensive patients still do not receive optimal therapy. For example, in African-American women over age 70, hypertension is said to be adequately controlled in only 33%.[28] Clearly, greater efforts must be made toward the delivery of optimal antihypertensive therapy.

HOPE trial: Is screening unnecessary?

Recent data from the Heart Outcomes Prevention Evaluation (HOPE) trial[29] further expand the role of ACE inhibitor therapy, from the attenuation of secondary ventricular remodeling to the primary prevention of LV dysfunction.[29] In 9,297 patients with vascular disease or diabetes and without LV dysfunction, those randomized to receive ramipril (10 mg once a day) had a substantially reduced risk of new-onset heart failure (9.1% vs 11.6% in the placebo group, relative risk 0.77, $P < .001$).

It may now be argued that all patients with a history of cardiovascular disease, regardless of the presence of LV dysfunction or hypertension, benefit from ACE inhibitor therapy. Results from the HOPE trial may therefore make screening for asymptomatic LV dysfunction unnecessary, because those with coronary artery disease should probably already be taking an ACE inhibitor.

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