**Diastolic Dysfunction in the Presence of Left Ventricular Systolic Dysfunction: Implications of β-Adrenergic Blocking Therapy**

Congestive heart failure is known to be caused by either left ventricular systolic dysfunction or diastolic dysfunction in patients with preserved left ventricular systolic performance. This differentiation in the pathophysiology of the clinical syndrome of congestive heart failure and the medical management of each of these unique hemodynamic conditions has been well described. However, despite the reports of abnormalities in left ventricular diastolic performance in patients with congestive heart failure who do not have left ventricular systolic dysfunction, no study has critically evaluated the prevalence, significance, and management of diastolic abnormalities in patients with left ventricular systolic dysfunction. Furthermore, the contribution of impairment in left ventricular diastolic performance in patients with impaired left ventricular systolic performance, as defined by a left ventricular ejection fraction of 40% or less, is underappreciated.

The development of novel therapeutic strategies aimed at the biologic properties of the failing heart through the use of β-adrenergic blocking therapy in chronic congestive heart failure has rekindled an interest in the investigation of diastole. This article summarizes the available data on diastolic dysfunction in the presence of congestive heart failure, in which left ventricular systolic dysfunction is assumed to predominate, with particular emphasis on the methods of assessment and response to β-adrenergic blocking therapy. In particular, the following questions will be addressed: 1) How often is diastolic dysfunction present when left ventricular systolic performance is impaired? 2) How do we identify diastolic dysfunction? 3) Is there any prognostic significance to impaired diastolic performance in this setting? and 4) Does medical therapy, principally β-adrenergic blockade, have a beneficial impact on abnormal left ventricular diastolic properties?

**Diastolic Abnormalities in Congestive Heart Failure**

In 1975, Waagstein and associates provided evidence that left ventricular diastolic dysfunction exists in the setting of congestive heart failure due predominantly to left ventricular systolic dysfunction when they...
demonstrated a strikingly prominent A wave and elevation of left ventricular end-diastolic pressure that subsequently improved with metoprolol therapy. Subsequent hemodynamic studies revealed a decrease in heart rate and left ventricular end-diastolic pressure with an associated increase in left ventricular ejection fraction with β-adrenergic blocking therapy. Other studies have assessed left ventricular diastolic filling as an index of hemodynamic impairment. Diastolic abnormalities were shown to correlate with symptoms, left ventricular filling pressures, and clinical outcomes such as death and transplantation. These investigations of left ventricular diastolic filling primarily involved noninvasive echocardiographic techniques, which are well reviewed in the literature.

Echocardiographic Assessment of Diastolic Performance

The evaluation of left ventricular diastolic performance typically begins with a Doppler echocardiographic examination of transmitral inflow velocities. Pulmonary venous flow velocities can also be used as an adjunct to the transmitral inflow velocities to assess filling pressures. Hemodynamic changes associated with advanced left ventricular diastolic dysfunction include an increased E wave (early) velocity, decreased A wave velocity (due to atrial contraction), and shortened deceleration time of the E wave velocity. Four distinct filling patterns (normal, delayed relaxation, pseudonormalized, and restrictive) have been described, representing the progression from normal to severe left ventricular diastolic dysfunction with increasing left ventricular chamber stiffness and high left ventricular filling pressures. These four phases describe a continuum of left ventricular diastolic dysfunction. As these echocardiographic phases progress in severity, the prognosis worsens.

When normal left ventricular filling is compromised, Doppler echocardiographic transmitral inflow velocities in the early stages reveal impaired left ventricular relaxation, as evidenced by a decrease in early transmitral inflow velocity (E wave) and an increased component of filling attributable to a greater dependence of left ventricular diastolic filling on atrial contraction (A wave). With progressive deterioration of left ventricular diastolic performance, the increasing left ventricular chamber stiffness and increasing left atrial pressure can result in a "pseudonormal" filling pattern, which can be unmasked by an assessment of the pulmonary venous velocities and through the use of the Valsalva maneuver. As left ventricular diastolic performance worsens, the most severe pattern is representative of restrictive physiology characterized by a rapid early filling component, a shortened deceleration time of the E wave velocity, a very stiff left ventricle with marked elevation in filling pressures, and a poor prognosis in terms of mortality and need for transplantation. Two newer echocardiographic modalities to assess left ventricular diastolic filling and performance are color kinesis and tissue Doppler imaging, but these have not yet become widely available.

Clinical data to support the use of echocardiographic techniques for assessing both the progression of left ventricular systolic and diastolic dysfunction and the response to medical therapy have been reported. In one study, reversion of the restrictive pattern, initially identified in 19 patients at baseline, was associated with a reduction in pulmonary capillary wedge pressure and improvement in exercise capacity following 6 months of medical therapy. In the six patients who initially had a nonrestrictive pattern at baseline and then developed a restrictive pattern, these hemodynamic features significantly deteriorated. In addition, progression to death or cardiac transplantation occurred in 35% of patients with a persistent restrictive pattern, 5% with a reversible restrictive pattern, and 4% with a persistent nonrestrictive pattern.

Despite technical advances in the echocardiographic evaluation of left ventricular diastolic performance, significant potential problems in techniques, measurement, and reporting should be noted. Furthermore, the potential for poor correlation with invasive descriptors of left ventricular diastolic performance and the confounding effects produced by changes in left ventricular preload, afterload, and heart rate on transmitral inflow velocities should always be considered.

β-Adrenergic Blocking Therapy: Insights into Modulation of Left Ventricular Diastolic Performance

In the late 1980s, the possibility that β-adrenergic receptor antagonists could modify left ventricular diastolic performance and that β-adrenergically mediated myocardial relaxation was attenuated in heart failure stimulated active investigation. Further insights were provided into the improvement in left ventricular diastolic properties with the consistent finding of a decrease in left ventricular end-diastolic pressure in the hemodynamic studies that followed Waagstein's initial report in 1975. In addition, chronic β-adrenergic blocking therapy was associated with improvement in the invasively determined time constant of exponential left ventricular pressure decay (τ), which is representative of early/active left ventricular relaxation. Noninvasive measurements of transmitral inflow velocities during β-adrenergic blockade showed an increase in the E wave deceleration time, which had been
shown to predict left ventricular chamber stiffness.\textsuperscript{27} Both the improvement in tau and the increase in echocardiographically demonstrated deceleration time from the early transmitral inflow velocity suggested improved left ventricular diastolic performance.

One noninvasive study\textsuperscript{28} did not find an effect on left ventricular diastolic performance with carvedilol therapy, perhaps because of the limitations of noninvasive assessments of left ventricular diastolic properties. In general, there appears to be supporting evidence for improved left ventricular diastolic performance in patients with left ventricular systolic dysfunction treated with \textbeta-\textadrenergic blocking agents. Furthermore, it appears that patients with the highest left ventricular end-diastolic pressures and most prolonged isovolumetric relaxation times may benefit the most from \textbeta-\textadrenergic blocking therapy.\textsuperscript{29} This finding strongly suggests the importance of diastolic modulation in the remarkable success of \textbeta-\textadrenergic blocking therapy in the treatment of patients with congestive heart failure, even in the presence of left ventricular systolic dysfunction.

**\textbeta-\textadrenergic Blocking Therapy and Congestive Heart Failure**

Nearly every placebo-controlled trial of \textbeta-\textadrenergic blocking therapy of greater than 3 months' duration has demonstrated improvement in left ventricular systolic performance.\textsuperscript{8} More prolonged therapy results in reverse remodeling, consisting of a regression in myocardial mass and normalization of left ventricular shape, which is partly a reversal of the cardiomyopathic phenotype.\textsuperscript{7,30} Given these changes in the phenotype with \textbeta-\textadrenergic blocking therapy, the possibility of improved clinical outcome exists. Traditional prognostic factors for clinical outcomes, such as progression to death or cardiac transplantation, have included left ventricular ejection fraction and total body peak oxygen consumption on exercise testing.

The clinical and echocardiographic data at the time of clinical presentation, such as the New York Heart Association functional class, left ventricular ejection fraction, and the various echocardiographic parameters of diastolic filling, were shown to be independently associated with subsequent progression to death or transplantation.\textsuperscript{31} In that investigation, 197 patients with dilated cardiomyopathy of both ischemic and nonischemic origin were assessed to derive a risk stratification score based on readily available clinical and echocardiographic parameters at the time of clinical presentation. According to stepwise regression analyses, age, echocardiographically derived peak E wave velocity, left ventricular ejection fraction, and systolic blood pressure independently predicted cardiac death. Similarly, the New York Heart Association functional class, left ventricular ejection fraction, the echocardiographically derived E/A wave ratio, and systolic blood pressure were independently associated with cardiac death or the need for cardiac transplantation. All of these clinical variables except for age can be affected by \textbeta-\textadrenergic blocking therapy.

The general consensus from the clinical trials\textsuperscript{32–38} involving \textbeta-\textadrenergic blockade in the treatment of patients with left ventricular systolic dysfunction is that the clinical benefits include decreased mortality, reduction in morbidity, and a tendency toward improvement of heart failure symptoms and exercise capacity. A greater mortality benefit is seen with \textbeta-\textadrenergic blocking therapy in these patients than with treatment by angiotensin-converting enzyme inhibitors. This benefit of \textbeta-\textadrenergic blocking therapy is also additive to the angiotensin-converting enzyme inhibitors, with the combined effect being greater than that of either alone.\textsuperscript{7}

**Hemodynamic Mechanism of Improvement in Left Ventricular End-Diastolic Pressure**

The hemodynamic mechanism of the \textbeta-\textadrenergic blocking therapy-induced improvement in left ventricular end-diastolic pressure, which can be used as a surrogate marker of left ventricular diastolic dysfunction in patients with congestive heart failure, presumably due to left ventricular systolic dysfunction, is unclear. We investigated the effects of metoprolol therapy on left ventricular diastolic performance in 18 patients (four patients served as controls) with idiopathic dilated cardiomyopathy to determine whether left ventricular diastolic dysfunction coexists in the setting of left ventricular systolic dysfunction, as defined by a left ventricular ejection fraction of 40% or less, and to assess the relationship between the decrease in left ventricular end-diastolic pressure and the modulation of left ventricular diastolic properties with metoprolol therapy.\textsuperscript{39} We also sought to determine if the anticipated improvement in left ventricular diastolic performance with \textbeta-\textadrenergic blocking therapy was independent or related to the changes in left ventricular systolic performance.

Left ventricular diastolic properties were assessed invasively, both before and following 6 months of metoprolol therapy (145±70 mg/day in two doses), with simultaneous micromanometry and bipline cineventriculography. In the metoprolol-treated group, the heart rate and left ventricular end-diastolic pressure decreased significantly, the left ventricular ejection
fraction and systolic arterial pressure increased significantly, and indices of left ventricular contractility improved significantly. These findings were similar to those previously reported. In patients who received metoprolol, all of the assessed left ventricular diastolic properties, i.e., isovolumic relaxation rate (tau), left ventricular chamber stiffness constant, left ventricular volume elastance, and myocardial stiffness constant, improved (Figs. 1 and 2). A multiple regression analysis revealed that the decrease in left ventricular end-diastolic pressure was a result of significant improvement in both early/active left ventricular relaxation (tau) and late/passive left ventricular relaxation (myocardial stiffness). The benefits on chamber stiffness and volume elastance were determined by improvement in the myocardial stiffness constant. Importantly, this suggested that the improvement in chamber compliance was not due to extraneous influences, e.g., venous return or pericardial restraint. The increase in the left ventricular ejection fraction was due to improvement in contractility. No improvement was seen in the control patients. These data indicate that improvement in left ventricular systolic performance occurs independently of improvement in left ventricular diastolic performance in response to ß-adrenergic blocking therapy. In addition, although both early/active and late/passive left ventricular relaxation contribute to improvement in left ventricular end-diastolic pressure, improvements

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HR=heart rate (beats/min); LVEDP=left ventricular end-diastolic pressure (mm Hg); LVSP=left ventricular systolic pressure (mm Hg); EDV=end diastolic volume (ml); ESV=end-systolic volume (ml); EF=left ventricular ejection fraction (%); (+)dP/dt<sub>max</sub>=peak positive dP/dt (mm Hg/sec); (+)dP/dt<sub>max</sub>/EDV=peak positive dP/dt/EDV (mm Hg/sec/ml); LV mass=left ventricular mass (g)

Figure 1. Early/active isovolumic left ventricular relaxation measures are improved with metprolol therapy. T<sub>1a</sub> and T<sub>2</sub>=relaxation constants.
documented by each invasive measurement of left ventricular diastolic performance occur independently. Whether or not there is a temporal dissociation in the benefits derived from β-adrenergic blocking therapy on left ventricular systolic and diastolic performance was not answered by this investigation, although it has been suggested that they are.25

Clinical Implications

The significance of this invasive hemodynamic investigation is that a strong relationship exists between the salutary effects of metoprolol therapy on left ventricular end-diastolic pressure, early/active isovolumic relaxation, and late/passive myocardial relaxation. Of particular note is that these effects occurred in addition to the beneficial effects of metoprolol on the left ventricular ejection fraction and contractility.

This somewhat parallel but independent improvement in left ventricular systolic and diastolic performance has also been detected by echocardiographic techniques.25 Our investigation of the hemodynamic mechanism underlying the reduction in left ventricular end-diastolic pressure with β-adrenergic blocking therapy also lends support to the finding of hemodynamic benefits occurring in both diastole and systole in patients with left ventricular systolic dysfunction, although they may be temporally disconnected.

Given that both left ventricular contractility and early/active isovolumic and late/passive myocardial relaxation are improved following β-adrenergic blocking therapy, a potential unifying pathophysiological mechanism may involve an effect of this therapy on abnormal calcium homeostasis in the cardiomyopathic myocyte. Abnormal calcium homeostasis possibly contributes to the hemodynamic correlates of increased myocardial stiffness, delayed isovolumic relaxation, and decreased contractility. The improvements in both left ventricular systolic and diastolic performance seen in this study, as in others, is consistent with the concept of β-adrenergic blocking therapy beneficially affecting calcium homeostasis.

Prevalence of Diastolic Dysfunction in the Presence of Left Ventricular Systolic Dysfunction

Returning to the issue of the prevalence of left ventricular diastolic dysfunction in patients with left ventricular systolic dysfunction, analysis of our data reveals that diastolic abnormalities are potentially very significant and common. In this small group of 14 cardiomyopathy patients, if a left ventricular end-diastolic pressure of 15 mm Hg or more was used as an index of left ventricular diastolic dysfunction, 11/14 patients (79%) could be considered to have diastolic abnormalities. If we use a more specific hemodynamic marker, such as the myocardial stiffness constant at a cut-off value of 6 or more, then the prevalence of left ventricular diastolic dysfunction decreases to 8/14 patients (57%). However, this still suggests that abnormalities in left ventricular diastolic properties are common in patients with left ventricular systolic dysfunction. These abnormalities in diastole can be readily assessed via noninvasive and invasive hemodynamic techniques. Each of these techniques has limitations, yet each has value, especially given the fact that noninvasive characterization of left ventricular diastolic properties has proven prognostic value and has been shown to correlate with clinical outcomes if it indicates improvement with medical therapy.

Conclusions

The beneficial effects of β-adrenergic blocking therapy in patients with ischemic or nonschemic cardiomyopathy due to left ventricular systolic dysfunction with or without concomitant diastolic dysfunction are clear, as manifested by an increase in left ventricular ejection fraction and a decrease in left ventricular end-diastolic pressure. These systolic-diastolic interactions may be connected through the β-adrenergic blocking effects on calcium homeostasis. The exact prevalence of left ventricular diastolic abnormalities in patients with left ventricular systolic dysfunction is unknown and requires further investigation. However, preliminary data would suggest that this is common.39 The mechanisms of the beneficial effects of β-adrenergic blockade in patients with left ventricular systolic dysfunction possibly include hemodynamic improvement in left ventricular diastolic properties, as demonstrated by favorable effects on early/active isovolumic and late/passive my-
occardial relaxation. The left ventricular end-diastolic pressure can be viewed as a marker for left ventricular diastolic dysfunction, which is potentially amenable to alteration with β-adrenergic blocking therapy. The potential importance of left ventricular diastolic performance and its modulation, and its relationship to improvement in left ventricular systolic performance, quality of life, and exercise performance, should be considered in future investigations.

References

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