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

The contribution of left ventricular diastolic dysfunction to the impairment in overall left ventricular performance in patients with systolic dysfunction is underappreciated. This article summarizes the available data on diastolic dysfunction in patients with congestive heart failure in which the predominant abnormality was thought to be left ventricular systolic dysfunction. The prevalence and identification of diastolic abnormalities and their clinical relevance are addressed, particularly the role of ß-adrenergic blocking therapy. The potential benefits of ß-adrenergic blocking therapy to diastolic performance are discussed from both a hemodynamic and clinical standpoint, with the implication that diastolic performance and its modulation should be considered in future investigations. (CHF. 2001;7:71–76)

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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.[1–4] 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,[5,6] 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 ß-adrenergic blocking therapy in chronic congestive heart failure[7,8] 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 ß-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[9] 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 ß-adrenergic blocking therapy.[10,11] Other studies have assessed left ventricular diastolic filling as an index of hemodynamic impairment.[12–16] Diastolic abnormalities were shown to correlate with symptoms,[12,13] left ventricular filling pressures,[14] and clinical outcomes,[13,15,16] such as death and transplantation. These investigations of left ventricular diastolic filling primarily involved noninvasive echocardiographic techniques, which are well reviewed in the literature.[17]

Echocardiographic Assessment of Diastolic Performance

The evaluation of left ventricular diastolic performance typically begins with a Doppler echocardiographic examination of transmitral inflow velocities.[18,19] 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[20] and the response to medical therapy[21] have been reported. In one study,[21] 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.[22] 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.[23]

ß-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.[24] 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[10,11] that followed Waagstein's initial report in 1975.[9] In addition, chronic ß-adrenergic blocking therapy was associated with improvement in the invasively determined time constant of exponential left ventricular pressure decay (tau), which is representative of early/active left ventricular relaxation.[10] Noninvasive measurements of transmitral inflow velocities during ß-adrenergic blockade showed an increase in the E wave deceleration time,[25,26] which had been

shown to predict left ventricular chamber stiffness.[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[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 ß-adrenergic 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 ß-adrenergic blocking therapy.[29] This finding strongly suggests the importance of diastolic modulation in the remarkable success of ß-adrenergic blocking therapy in the treatment of patients with congestive heart failure, even in the presence of left ventricular systolic dysfunction.

ß-Adrenergic Blocking Therapy and Congestive Heart Failure

Nearly every placebo-controlled trial of ß-adrenergic blocking therapy of greater than 3 months' duration has demonstrated improvement in left ventricular systolic performance.[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.[7,30] Given these changes in the phenotype with ß-adrenergic 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.[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 ß-adrenergic blocking therapy.

The general consensus from the clinical trials[32–38] involving ß-adrenergic 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 ß-adrenergic blocking therapy in these patients than with treatment by angiotensin-converting enzyme inhibitors. This benefit of ß-adrenergic blocking therapy is also additive to the angiotensin-converting enzyme inhibitors, with the combined effect being greater than that of either alone.[7]

Hemodynamic Mechanism of Improvement in Left Ventricular End-Diastolic Pressure

The hemodynamic mechanism of the ß-adrenergic 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.[39] We also sought to determine if the anticipated improvement in left ventricular diastolic performance with ß-adrenergic 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 biplane cineventriculography. In the metoprolol-treated group, the heart rate and left ventricular end-diastolic pressure decreased significantly, the left ventricular ejection

TABLE. HEMODYNAMIC INDICES

Patient	HR		LVEDP		LVSP		DV		ESV		EF		(+)dP/dt$_{max}$		(+)dP/dt$_{max}$/EDV		LV mass	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Metoprolol-Treated Cardiomyopathy Patients																		
1	65	47	24	18	134	139	254	247	185	160	27.2	35.2	747	928	2.94	3.76	219	296
2	95	55	32	11	119	126	239	197	180	91	24.7	53.8	817	863	3.42	4.38	226	229
3	80	62	31	24	108	153	178	159	115	86	35.4	45.9	841	1161	4.72	7.30	137	209
4	107	83	26	12	96	99	494	358	382	255	22.7	28.8	835	827	1.69	2.31	281	199
5	92	54	15	14	101	128	219	139	143	51	34.7	63.3	623	1374	2.84	9.88	227	147
6	88	80	5	9	103	121	177	187	100	116	43.5	38.0	827	1096	4.67	5.86	124	160
7	49	60	21	12	134	126	221	169	120	95	43.1	43.8	1192	1258	5.65	7.44	167	186
8	79	73	17	16	98	103	140	146	74	81	47.2	44.5	776	1160	4.79	4.28	159	126
9	72	85	16	12	114	109	415	346	272	229	34.5	33.8	609	744	1.47	2.15	175	223
10	87	88	13	9	110	113	262	191	168	78	35.9	59.2	1032	1047	3.94	5.48	287	222
11	80	83	12	10	114	122	200	215	104	66	48.0	69.3	1295	1592	6.48	7.40	205	170
12	86	60	29	15	88	95	600	250	503	164	16.2	34.4	498	711	0.83	2.84	345	316
13	83	84	23	9	116	134	347	252	240	159	30.8	36.9	836	996	2.41	3.95	302	247
14	70	70	28	12	111	106	429	399	344	337	19.8	15.5	688	676	1.57	1.69	384	425
Mean	81	70	21	13	110	120	298	233	209	141	33.1	43.0	830	1031	3.39	4.91	231	225
SD	14	14	8	4	13	16	138	82	126	83	10.1	14.5	218	265	1.71	2.42	79	78
Control Cardiomyopathy Patients																		
1	90	79	24	22	140	171	278	174	200	207	28.1	24.5	904	1195	3.25	4.36	211	198
2	82	67	18	19	105	106	427	377	287	252	32.8	33.2	648	587	1.52	1.56	191	245
3	75	83	35	28	104	90	379	372	288	279	24.0	25.0	655	678	1.73	1.82	171	220
4	77	96	21	20	137	124	339	271	217	175	36.0	35.4	1233	1284	3.64	4.74	198	176
Mean	81	81	25	22	122	123	356	324	248	228	30.2	29.5	860	936	2.53	3.12	193	210
SD	7	12	7	4	20	35	63	59	46	46	5.3	5.6	276	354	1.07	1.66	17	30

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$_{max}$=peak positive dP/dt (mm Hg/sec); (+)dP/dt$_{max}$/EDV=peak positive dP/dt/EDV (mm Hg/sec/ml); LV mass=left ventricular mass (g)

fraction and systolic arterial pressure increased significantly, and indices of left ventricular contractility improved significantly (Table). These findings were similar to those previously reported.[39] 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

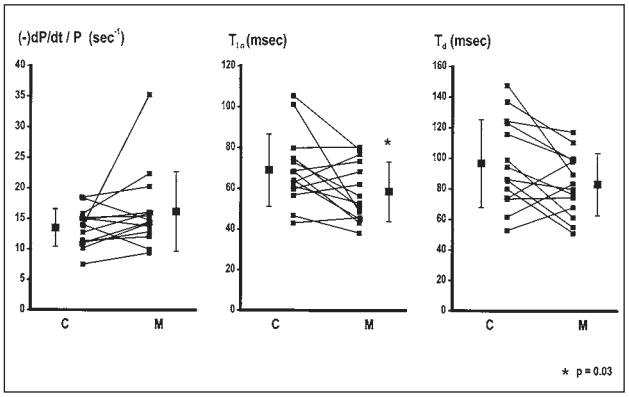

Figure 1. Early/active isovolumic left ventricular relaxation measures are improved with metprolol therapy. T_{ln} and T_d=relaxation constants.

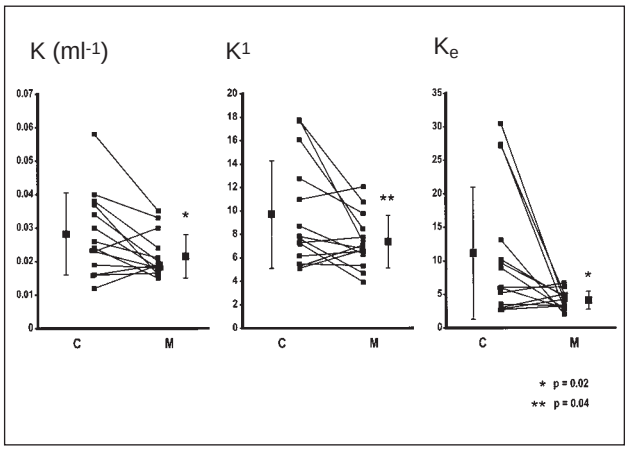

Figure 2. Late/passive myocardial relaxation properties are beneficially affected by metoprolol therapy. k=left ventricular chamber stiffness constant; k^1=left ventricular volume elastance; k_e=myocardial stiffness constant.

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 ß-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 metropolol 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 ß-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 ß-adrenergic blocking therapy, a potential unifying pathophysiologic 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 ß-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 ß-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 ß-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 ß-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-

ocardial 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 ß-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.

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