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Restrictive Left Ventricular Filling Patterns Are Predictive of Diastolic Ventricular Interaction in Chronic Heart Failure

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Objectives. **The purpose of this study was to determine whether restrictive left ventricular (LV) filling patterns are associated with diastolic ventricular interaction in patients with chronic heart failure.**

Background. **We recently demonstrated a diastolic ventricular interaction in ~50% of a series of patients with chronic heart failure, as evidenced by paradoxic increases in LV end-diastolic volume despite reductions in right ventricular end-diastolic volume during volume unloading achieved by lower body negative pressure (LBNP). We reasoned that such an interaction would impede LV filling in mid and late diastole, but would be minimal in early diastole, resulting in a restrictive LV filling pattern.**

Methods. **Transmitral flow was assessed using pulsed wave Doppler echocardiography in 30 patients with chronic heart failure and an LV ejection fraction ≤35%. Peak early (E) and atrial (A) filling velocities and E wave deceleration time were measured. Left ventricular end-diastolic volume was measured using radionuclide ventriculography before and during −30-mm Hg LBNP.**

Results. **Nine of the 11 patients with and 2 of the 16 patients without restrictive LV filling patterns (E/A >2 or E/A 1 to 2 and E wave deceleration time ≤140 ms) increased LV end-diastolic volume during LBNP ($p = 0.001$). The change in LV end-diastolic volume during LBNP was correlated with the baseline A wave velocity ($r = -0.52$, $p = 0.005$) and E/A ratio ($r = 0.50$, $p = 0.01$).**

Conclusions. **Restrictive LV filling patterns are associated with diastolic ventricular interaction in patients with chronic heart failure. Volume unloading in the setting of diastolic ventricular interaction allows for increased LV filling. Identifying patients with chronic heart failure and restrictive filling patterns may therefore indicate a group likely to benefit from additional vasodilator therapy.**

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In a recent study, we demonstrated that diastolic ventricular interaction mediated by pericardial constraint is important in some patients with chronic heart failure (1). This interaction was inferred by the observation of an apparently paradoxic increase in left ventricular (LV) end-diastolic volume in ~50% of patients during central blood volume unloading, despite a decrease in right ventricular (RV) end-diastolic volume and right atrial pressure (Fig. 1). In these patients, LV filling was impeded by external forces (i.e., the pericardium and RV); the reduction in RV volume that occurred during acute volume unloading then allowed for improved LV filling and therefore an increase in LV end-diastolic volume. We reasoned that such an interaction is likely to be minimal in early diastole (when both ventricles are small) but will progressively increase as both chambers enlarge and be maximal at end-diastole (2). We therefore hypothesized that these patients would exhibit restrictive LV filling patterns, a finding known to indicate clinical severity of heart failure (3–12). Restrictive LV filling could then be used as a marker indicating important diastolic ventricular interaction in patients with chronic heart failure. The presence of such an interaction may have important therapeutic implications (1,13–16).

To test this hypothesis, we studied LV filling using Doppler echocardiography of transmitral flow in 30 patients with chronic heart failure. We used a previously reported radionuclide technique to assess LV end-diastolic volume before and during acute volume unloading achieved by the application of −30 mm Hg of lower body negative pressure (LBNP). We inferred diastolic ventricular interaction in those patients in whom LV volume increased during LBNP.

Methods

Subjects. We studied 30 patients with chronic heart failure who met the following inclusion criteria: symptomatic or asymptomatic LV dysfunction of at least 3 months' duration;

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Abbreviations and Acronyms

LBNP = lower body negative pressure
LV = left ventricle, left ventricular
RV = right ventricle, right ventricular

LV ejection fraction ≤35% at entry; and no objective change in the patients' clinical status or cardioactive drug therapy over the previous 2 weeks. The following exclusion criteria were applied: structural valvular heart disease; previous open heart surgery; known pericardial disease; rhythm other than sinus; myocardial infarction within 6 months; and current unstable angina.

Study protocol. The investigations were performed at the Royal Brisbane Hospital with the approval of the hospital's Ethics Committee. Written informed consent was obtained from all patients. The studies were performed ~2 h after lunch. Diuretic agents were omitted on the day of the study, but other cardioactive medications were continued. Echocardiographic studies were performed immediately before radionuclide ventriculography. All Doppler and radionuclide studies were analyzed off-line by two different investigators who had no knowledge of the patients' clinical status or the results of the other studies performed.

Echocardiography. A Hewlett-Packard phased array scanner with a 2.5-MHz transducer was used for pulsed wave Doppler recordings. These recordings were obtained during relaxed end-expiration with the patient lying supine at rest. Transmitral flow was recorded in the standard apical four-chamber view with the sample volume positioned between the tips of the mitral leaflets (4,17,18). The peak velocity in early diastole (E wave) and at atrial contraction (A wave) and the deceleration time of the E wave were measured. The E wave deceleration time was obtained by extrapolating the initial slope of E wave deceleration to the zero line (4,17,18). Cardiac cycles were excluded if the descent of the E wave was curvilinear or if there was fusion of early mitral flow velocity and flow velocity at atrial contraction. The ratio of the peak velocities of the E and A waves was derived. Repeated analysis was performed in 16 patients: the coefficient of variation for measurement of the E wave velocity was 7.2%, A wave velocity 6.4%, E/A ratio 5.2% and E wave deceleration time 4.5%. Mitral regurgitation was assessed by color flow Doppler echocardiography using a 2.5-MHz transducer and if present, was semiquantitatively graded on a scale of one to four (19).

We used a standard definition of restrictive LV filling: patients with an E/A ratio >2 or 1 to 2 with an E wave deceleration time ≤140 ms were classified as having restrictive LV filling patterns (5,12). This definition was determined before the onset of the study. In view of a recent study demonstrating that a short (≤125 ms) E wave deceleration time was a powerful independent predictor of a poor prognosis in patients with LV systolic dysfunction (5), we also classified the patients according to whether or not their deceleration time was ≤125 ms (this definition was not determined before the onset of the study).

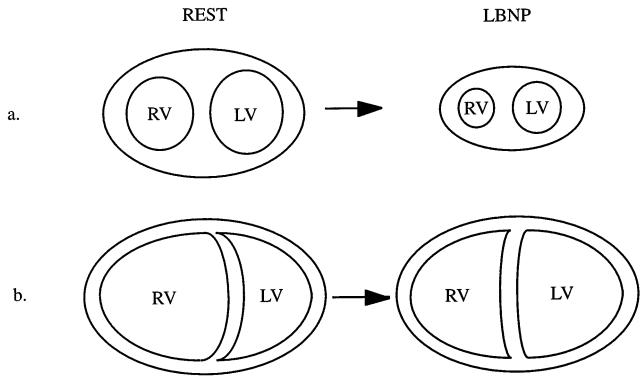

Figure 1. A schematic representation of the changes in ventricular volumes that occur during acute volume unloading such as that produced by the application of LBNP. **a,** In normal subjects, a diastolic ventricular interaction is minimal. Therefore, both RV and LV volumes decrease. **b,** In some patients with chronic heart failure, LV filling is constrained by the surrounding RV and pericardium. The decrease in RV volume that occurs during acute volume unloading then allows for increased LV filling. Thus, LV volume increases. This phenomenon is referred to as a direct diastolic ventricular interaction.

Radionuclide ventriculography. We used a technique we have previously described to demonstrate diastolic ventricular interaction in heart failure (1). Radionuclide ventriculography was performed before and during −30 mm Hg LBNP, using a modified in vivo technique to label red blood cells with 925 MBq technetium-99m pertechnetate. After 20 min of rest, a 4-min cardiac scintigram was obtained in the left anterior oblique view using a small field-of-view gamma camera (GE 300A, GE Medical Systems) fitted with a low energy, general purpose, parallel-hole collimator and interfaced to a dedicated computer system (Max Delta, Siemens). Lower body negative pressure of −30 mm Hg was applied for 5 min; in the final 4 min the scintigraphy was repeated. Venous blood samples (10 ml) were obtained to determine blood activity during each acquisition. Background-corrected LV end-diastolic counts were determined using a semiautomated edge-detection algorithm and corrected for decay, blood activity and tissue attenuation to allow for determination of LV end-diastolic volume (20). Background-corrected RV end-diastolic counts were determined manually with the aid of stroke volume, ejection fraction and paradoxic images. Corrections were made for decay and blood activity to allow for determination of the change in RV end-diastolic volume during LBNP. A diastolic ventricular interaction was implied if there was an increase in LV end-diastolic volume during LBNP greater than the coefficient of variation for replicate measurements (i.e., >3.1%). Sixteen patients had a 5F catheter inserted through the brachial vein to measure right atrial pressure and hence the degree of central blood volume unloading achieved by LBNP. Right atrial pressure was measured using a Baxter pressure transducer referenced to atmosphere at the mid-axillary line and connected to a Hewlett-Packard multichannel recorder.

Table 1. Baseline Characteristics

Age (years)	53 ± 11
Gender (M/F)	25/5
Medications	
ACE inhibitors	25
Diuretic agents	20
Digoxin	14
Nitrates	10
Hydralazine	10
Beta-blockers	4
Amiodarone	4
LVEF (%)	20 ± 8
Peak E wave velocity (m/s)	0.69 ± 0.25
Peak A wave velocity (m/s)	0.54 ± 0.20
E/A ratio	1.5 ± 1.0
E wave deceleration time (ms)	151 ± 52

Data are expressed as mean value ± SD or number of patients. A wave = atrial (late) component of transmitral diastolic flow; ACE = angiotensin-converting enzyme; E wave = early component of transmitral diastolic flow; E/A ratio = ratio of E wave to A wave peak velocity; LVEF = left ventricular ejection fraction.

Statistical analysis. All data are expressed as the mean value ± SD. Paired *t* tests were used to compare observations before and during LBNP. The Mann-Whitney rank-sum test was used to compare the New York Heart Association functional class between the two groups of patients. Two-sample *t* tests were used to compare other characteristics. Bonferroni corrections were applied for multiple comparisons. Linear regression analysis was used to assess correlations between changes in LV end-diastolic volume and baseline Doppler echocardiographic characteristics. The Fisher exact test was used to compare the proportion of patients who increased LV end-diastolic volume, classified according to their LV filling pattern. Statistical significance was assumed at $p < 0.05$.

Results

The group consisted of 25 men and 5 women (mean age 53 ± 11 years). The baseline characteristics and echocardiographic data are described in Table 1. Eighteen patients had dilated cardiomyopathy and 12 had ischemic heart disease. Seven patients were in New York Heart Association functional class I, 16 in class II and 7 in class III.

Eleven patients were classified as having restrictive and 16 as having nonrestrictive LV filling patterns. We were unable to classify three patients because of fusion of early mitral flow velocity and flow velocity at atrial contraction. Comparisons of baseline characteristics in patients with restrictive and nonrestrictive LV filling patterns are described in Table 2. Patients with restrictive filling patterns were more symptomatic according to New York Heart Association functional classification, had a higher diastolic and mean arterial blood pressure and larger RV end-diastolic volume and had a tendency toward a higher heart rate and higher right atrial pressure than patients with nonrestrictive filling patterns. Baseline LV end-diastolic volume and LV ejection fraction were similar in both groups.

Table 2. Comparisons of Baseline Characteristics in Patients With Restrictive and Nonrestrictive Left Ventricular Filling Patterns

	Restrictive (n = 11)	Nonrestrictive (n = 16)	p Value
Age (years)	52 ± 11	54 ± 9	0.55
NYHA functional class			0.04
I	2	5	
II	4	11	
III	5		
HR (beats/min)	80 ± 17	72 ± 12	0.15
SAP (mm Hg)	107 ± 13	105 ± 15	0.81
DAP (mm Hg)	71 ± 9	59 ± 9*	0.004
MAP (mm Hg)	82 ± 9	73 ± 11	0.03
MRAP (mm Hg)	11.4 ± 6.2 (n = 8)	7.8 ± 1.7 (n = 6)	0.19
LVEDV (ml)	292 ± 79	296 ± 85	0.91
RVEDV (volume equivalents)	52 ± 19	32 ± 7*	0.001
LVEF (%)	20 ± 9	21 ± 7	0.65

*$p < 0.05$ after correction for multiple comparisons. Data are expressed as mean value ± SD or number of patients. DAP = diastolic (systemic) arterial pressure; HR = heart rate; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; MAP = mean (systemic) arterial pressure; MRAP = mean right atrial pressure; NYHA = New York Heart Association; RVEDV = right ventricular end-diastolic volume; SAP = systolic (systemic) arterial pressure.

During LBNP, there were significant reductions in mean right atrial pressure (10.1 ± 5.0 to 7.3 ± 5.3 mm Hg, $p < 0.001$; n = 16) and RV end-diastolic volume (39 ± 16 to 33 ± 16 volume equivalents, $p < 0.001$) consistent with central blood volume unloading. Left ventricular end-diastolic volume tended to increase (293 ± 77 to 299 ± 76 ml, $p = 0.09$), with a wide variation between the patients (range −24 to 48 ml). Changes occurring during LBNP in patients classified according to their LV filling pattern are described in Table 3. Left ventricular end-diastolic volume increased during LBNP in patients with restrictive filling patterns (292 ± 79 to 308 ± 82 ml, $p < 0.01$) and tended to decrease in patients with nonrestrictive filling patterns (296 ± 85 to 292 ± 80 ml, $p = 0.35$). Although the changes in LV end-diastolic volume during LBNP were significantly different between the two groups of

Table 3. Comparisons of Changes During Lower Body Negative Pressure in Patients With Restrictive and Nonrestrictive Left Ventricular Filling Patterns

	Restrictive (n = 11)	Nonrestrictive (n = 16)	p Value
HR (beats/min)	−0.5 ± 4.5	+2.0 ± 5.2	0.22
SAP (mm Hg)	−0.1 ± 8.4	−1.5 ± 10.5	0.73
DAP (mm Hg)	−0.6 ± 5.0	+0.7 ± 7.4	0.65
MAP (mm Hg)	−0.9 ± 7.1	−0.2 ± 6.8	0.81
MRAP (mm Hg)	−2.7 ± 1.1 (n = 8)	−2.9 ± 0.8 (n = 6)	0.65
LVEDV (ml)	+15.9 ± 15.3	−3.3 ± 14.0*	0.002
RVEDV (volume equivalents)	−5.6 ± 3.1	−5.8 ± 3.5	0.89

*$p < 0.05$ after correction for multiple comparisons. Data are expressed as mean value ± SD. Abbreviations as in Table 2.

patients, the reductions in RV end-diastolic volume and right atrial pressure were similar.

We classified the patients according to whether or not they increased LV end-diastolic volume during LBNP. Patients who increased LV volume were presumed to have important diastolic ventricular interaction. Nine of the 11 patients with and 2 of the 16 patients without restrictive LV filling patterns increased LV end-diastolic volume during LBNP ($p < 0.001$). A restrictive LV filling pattern, therefore, had 82% sensitivity and 88% specificity for detecting diastolic ventricular interaction as predefined in this study. The patients were also classified according to their E wave deceleration time. Eight of the 9 patients with an E wave deceleration time ≤125 ms and 3 of the 18 patients with an E wave deceleration time >125 ms increased LV end-diastolic volume during LBNP ($p < 0.001$). Two of the three patients who could not be classified in view of fusion of early mitral flow velocity and flow velocity at atrial contraction exhibited an increase in LV volume; the deceleration time was <140 ms in both these patients. The deceleration time in the remaining patient was >140 ms.

There were significant correlations on univariate analysis between the change in LV end-diastolic volume during LBNP and the baseline A wave velocity ($r = -0.52$, $p = 0.005$) and E/A ratio ($r = 0.50$, $p < 0.01$). Two patients were classified as having grade 2-3/4 and three patients were graded as having grade 2/4 mitral regurgitation. All other patients had either mild or no mitral regurgitation. After removal of these five patients from the analysis, significant correlations remained between the change in LV end-diastolic volume and the baseline A wave velocity ($r = -0.59$, $p < 0.005$) and E/A ratio ($r = 0.54$, $p < 0.01$).

Discussion

Left ventricular filling patterns are determined by numerous factors, including left atrial pressure, LV relaxation and compliance, mitral valve area, diastolic ventricular interaction and pericardial constraint (21–24). The pattern of LV filling observed in patients with chronic heart failure varies as a result of these factors. Patients with restrictive filling patterns are more symptomatic (6,8,10), have reduced exercise capacity (3) and have an increased risk of death or the need for a heart transplant (5–7,9,11,12). In our study, we have demonstrated that diastolic ventricular interaction is common in such patients. Nine of the 11 patients with restrictive LV filling patterns increased LV end-diastolic volume during acute volume unloading achieved by the application of LBNP. This occurred despite associated reductions in RV volume and right atrial pressure. In contrast, only 2 of the 16 patients with nonrestrictive filling patterns increased LV volume. Hence, restrictive LV filling patterns had a high sensitivity and specificity for detecting diastolic ventricular interaction in these patients with chronic heart failure.

Diastolic ventricular interaction in chronic heart failure. Diastolic ventricular interaction refers to the situation where the diastolic volume of one ventricle directly influences the filling of the other ventricle (1,13,15,16,25). Experimentally, such an interaction appears to be mediated, at least in part, by the pericardium (26,27). Normally, pericardial constraint to ventricular filling is minimal and acute volume unloading causes a reduction in both LV and RV end-diastolic volumes (1). In chronic heart failure, the increased filling pressures may distend the ventricles to such an extent that the filling of the LV is impeded by the surrounding pericardium and RV. In this setting, diastolic ventricular interaction is enhanced. The reduction in RV end-diastolic volume that occurs during acute volume unloading allows for increased LV filling and hence an increase in LV end-diastolic volume (1). Similarly, in the present study, over one-third of the patients studied developed an increase in LV end-diastolic volume despite associated reductions in RV end-diastolic volume, indicating a significant diastolic ventricular interaction in these patients.

We have previously observed that patients who increased LV end-diastolic volume during LBNP have higher pulmonary capillary wedge pressures (1). Similarly, restrictive LV filling is associated with raised pulmonary capillary wedge pressure in patients with chronic heart failure (4,6,10). Transmitral flow is determined, however, by the atrioventricular gradient throughout diastole (17,22,23); therefore, LV diastolic pressure is equally important in determining the transmitral gradient and hence flow. Dauterman et al. (28) have previously observed the important contribution of external force provided by the pericardium and RV to the measured intracavitary LV diastolic pressure in a variety of situations including dilated cardiomyopathy. We would therefore suggest that in heart failure patients in whom diastolic ventricular interaction is enhanced, the contribution of external forces to intracavitary LV diastolic pressure may at least partly explain restrictive LV filling patterns. In early diastole, ventricular volume will be smallest; therefore, external constraint to LV filling will be minimal. In late diastole, however, further LV filling will be limited by the surrounding pericardium and RV, resulting in diminished late diastolic filling (2,24). Hence, the transmitral gradient will be high at the onset of diastole but will rapidly diminish thereafter, resulting in a restrictive filling pattern. Consistent with this is the observed association between restrictive LV filling and pericardial constriction (29). In contrast, restrictive filling is rarely observed in patients with pericardial tamponade because in this condition, constraint to LV filling occurs throughout diastole (30).

It is likely that central blood volume unloading sufficient to abolish a diastolic ventricular interaction will tend to normalize restrictive LV filling patterns. A recent study by Pozzoli et al. (7), examining the effects of nitroprusside infusion on transmitral flow in patients with chronic heart failure, demonstrated variable responses. Indeed, they identified a subgroup of patients in whom restrictive LV filling patterns were maintained despite a volume reduction, and these patients had a poorer outlook compared with those patients in whom restrictive filling patterns were normalized. The amount of volume unloading required to normalize restrictive LV filling patterns would vary depending on loading conditions, myocardial com-

pliance and the degree of ventricular interaction present. Further studies examining the effects of incremental volume unloading on transmitral flow in patients with heart failure may help to address this.

Study limitations. A number of confounding variables may affect LV filling, including age, heart rate and mitral regurgitation (6,10,31,32). In our study, patients with and without restrictive LV filling patterns were of similar age. Tachycardia may increase A wave velocity, but patients with restrictive filling patterns tended to have a higher heart rate; therefore, this is not the explanation. Similarly, mitral regurgitation does not explain the variation in LV filling. Excluding those patients with more than mild mitral regurgitation did not affect the final results.

The majority of patients in this study were taking angiotensin-converting enzyme inhibitors and diuretic agents. The conclusions reached may therefore not necessarily apply to heart failure patients receiving no medical therapy. However, our results do apply to a treated group, which is more relevant to contemporary clinical practice.

We observed an association between restrictive LV filling patterns and diastolic ventricular interaction in patients with chronic heart failure. Although we suggest that a ventricular interaction may contribute to restrictive LV filling by influencing the transmitral gradient throughout diastole, we acknowledge that other factors may also be important, including loading conditions and reduced intrinsic LV myocardial compliance. The relative contribution of these factors in determining LV filling was not assessed in this study. In addition, LV pressure in early diastole is a function of so-called diastolic suction (33). Interestingly, Tyberg et al. (34) recently presented preliminary data that associate a restrictive filling pattern with increased diastolic suction in dogs with pacing-induced heart failure. Although their findings are unexpected and await confirmation, they may provide new insight into these mechanisms.

Tissue attenuation was assessed with reference to the center of the LV. We were therefore unable to calculate RV end-diastolic volume in absolute units, but were able to determine the relative change in RV end-diastolic volume during LBNP. The observed increase in LV end-diastolic volume in association with a reduction in RV end-diastolic volume during volume unloading nevertheless indicates the presence of a diastolic ventricular interaction in those patients.

Clinical implications. Assuming a causal relation, a diastolic ventricular interaction may provide an explanation for why restrictive LV filling patterns are associated with increased mortality and reduced exercise capacity in patients with chronic heart failure. We have previously proposed that a diastolic ventricular interaction may contribute to cardiac baroreflex dysfunction in chronic heart failure (35), and we have confirmed an association between the two in a recent study (36). Baroreflex dysfunction is associated with increased mortality in patients with heart failure (37). Furthermore, neurohumoral activation in heart failure is probably largely due to reduced baroreceptor activity (38,39). Janicki (40) observed that during exercise, stroke volume becomes invariant in chronic heart failure patients with a diastolic ventricular interaction. Given that chronotropic incompetence is common in such patients, cardiac output augmentation (and hence exercise capacity) will be markedly impaired.

Dornhorst et al. (25) proposed that a change in LV volume occurring as a result of a diastolic ventricular interaction would result in a proportional change in stroke volume, as one would predict according to Frank-Starling mechanisms. Consistent with this, Belenkie et al. (13) observed that volume unloading in an animal model of acute pulmonary hypertension caused a reduction in RV diastolic dimension and an increase in both LV diastolic dimension and stroke work. This highlights the importance of venodilator therapy, which, by decreasing RV end-diastolic volume, may increase LV end-diastolic volume and stroke volume in those heart failure patients with a diastolic ventricular interaction. This may explain why stroke volume is maintained or increases when pulmonary capillary wedge pressure is lowered with vasodilator therapy in some patients with chronic heart failure (41,42), even when systemic vascular resistance remains unchanged (42). Clinicians often use serial invasive hemodynamic assessment to tailor therapy in patients with chronic heart failure. Determination of transmitral flow may therefore provide a noninvasive alternative to identify those heart failure patients likely to benefit from additional vasodilator therapy.

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