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ORIGINAL RESEARCH

Loss of Adrenergic Augmentation of Diastolic Intra-LV Pressure Difference in Patients With Diastolic Dysfunction

Evaluation by Color M-Mode Echocardiography

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OBJECTIVES The aim of this study was to evaluate the hypothesis that the adrenergic response of the intraventricular pressure difference (IVPD) is reduced in patients with preserved ejection fraction (EF) and diastolic dysfunction (DD).

BACKGROUND In early diastole, there is a progressive IVPD extending from the left atrium (LA) to the left ventricular (LV) apex. In response to adrenergic stimulation, as occurs during exercise, the IVPD increases allowing rapid filling without an abnormal increase in LA pressure. Patients with heart failure with a reduced EF have impaired adrenergic augmentation of the IVPD.

METHODS We studied 166 consecutive patients undergoing dobutamine stress echocardiography who had no inducible ischemia and an EF ≥50%, of which 21 had normal diastolic function, 14 had impaired relaxation (grade 1), 80 had pseudonormal filling (grade 2), and 51 had restrictive filling (grade 3). Color M-mode Doppler (CMMD) images of mitral inflow were obtained at rest and during low (10 μg/kg/min) and peak (20 to 40 μg/kg/min) doses of dobutamine. The total IVPD from the LA to LV apex, LA to mid-LV, and mid-LV to the LV apex were calculated using the CMMD data to integrate the Euler equation.

RESULTS Total IVPD was not different between groups at rest. With dobutamine, the total IVPD increased by 2.20 ± 1.95 mm Hg in normal subjects and by only 0.73 ± 1.33 mm Hg, 1.84 ± 1.63 mm Hg, and 1.08 ± 1.57 mm Hg in patients with grades 1, 2, and 3 DD, respectively. This difference was due to a failure in augmentation of IVPD from the mid-LV to the LV apex, indicating reduced apical ventricular suction with DD, whereas the IVPD from the LA to the mid-LV responded similarly to dobutamine in normal subjects and those with DD.

CONCLUSIONS In patients with preserved EF, DD is associated with a reduced adrenergic augmentation of the IVPD from the mid-LV to the LV apex, reflecting less apical suction. (J Am Coll Cardiol Img 2012;5:861–70) © 2012 by the American College of Cardiology Foundation

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In early diastole, rapid left ventricular (LV) relaxation and recoil of elastic elements that were compressed during ejection produced a progressive intraventricular pressure difference (IVPD) extending from the left atrium (LA) to the apex of the LV (1). This IVPD rapidly accelerates blood into the LV in early diastole (1). In response to adrenergic stimulation, as occurs during exercise, the early diastolic IVPD normally increases due to a decrease in minimum LV pressure, allowing for more rapid filling without an abnormal increase in LA pressure (2–4). This larger IVPD results from both ejection to lower end-systolic volume and more rapid LV relaxation. Patients with heart failure (HF) and reduced ejection fraction (EF) have a reduced response to adrenergic stimulation due to down-regulation and uncoupling of beta receptors (5–7). As a result, in HF with reduced EF, the decrease of early diastolic LV pressure in response to adrenergic stimulation is reduced (2,8,9). Thus, the exercise-induced increased early diastolic filling rate in patients with reduced EF is dependent upon an increase in LA pressure (9). The reduction of IVPD in patients with reduced EF is due to both reduced inertial acceleration and increased convective deceleration from a dilated ventricle (2).

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ABBREVIATIONS AND ACRONYMS

a′ = late diastolic mitral annular velocity

CMMD = color M-mode Doppler

e′ = early diastolic mitral annular velocity

EF = ejection fraction

HF = heart failure

HFpEF = heart failure with a preserved ejection fraction

IVPD = intraventricular pressure difference

LA = left atrium/atrial

LV = left ventricle/ventricular

s′ = systolic mitral annular velocity

An abnormal increase in LA pressure during exercise is also present in patients with HF and a preserved EF (10). However, the IVPD response in patients with diastolic dysfunction and preserved EF is unknown. We hypothesize that the response of IVPD to adrenergic stimulation is reduced in patients with diastolic dysfunction and preserved EF. Accordingly, we noninvasively evaluated the IVPD and its spatial distribution in patients with preserved EF and diastolic filling abnormalities during dobutamine stress echocardiography.

METHODS

Patients. This study was approved by the institutional review boards of Wake Forest School of Medicine and Virginia Tech. Patients at Wake Forest Baptist Medical Center referred for clinically indicated pharmacological stress echocardiography were eligible for this study. Patients with an EF <50%, inducible ischemia, or poor echo images were excluded. We also excluded the patients with significant mitral regurgitation or stenosis, a prosthetic mitral valve, constrictive pericarditis, and dyssynchrony in which E/e′ is not reliable.

Echocardiography. Echocardiography was performed using an iE33 ultrasound system with a multiple frequency transducer (Philips Medical Systems, Andover, Massachusetts). Before stress echocardiography, patients had a complete transthoracic echocardiogram. LV end-diastolic volume, end-systolic volume, stroke volume, and EF were calculated by the modified Simpson method using an apical 4-chamber view. Doppler echocardiographic variables were recorded as previously reported (11).

Dobutamine stress echocardiography was performed according to a standard protocol (12). Beta-blockers were stopped the morning of the examination. After obtaining baseline observations, dobutamine was infused at 10 μg/kg/min and increased by 10 μg/kg/min every 3 min up to 40 μg/kg/min to obtain 80% of the age-predicted maximum heart rate or clinically relevant symptoms (chest pain or dyspnea), electrocardiogram change, hypotension, or hypertension (systolic blood pressure >240 mm Hg). If the target heart rate was not obtained at the maximum infusion rate (40 μg/kg/min), atropine sulfate was infused. In addition to standard images to evaluate LV wall motion, color M-mode Doppler (CMMD) images, transmitral inflow Doppler, and tissue Doppler of mitral annular motion were obtained at rest, and during low- and peak-dose dobutamine infusion. CMMD images were recorded with a cursor parallel to mitral inflow in an apical 4-chamber view.

Diastolic function was assessed as: grades 1 (impaired relaxation), 2 (pseudonormal filling), and 3 (restrictive filling) according to the European Association of Echocardiography/American Society of Echocardiography recommendations (11).

Hemodynamics. The heart rate and systolic and diastolic blood pressure were recorded at rest, and during the low- and peak-dose infusion of dobutamine. Using these data and stroke volume, hemodynamic parameters, such as systemic vascular resistance, systemic arterial compliance, and effective aortic elastance, were calculated (see Online Appendix A for additional information).

IVPD measurement. The CMMD images were analyzed in MATLAB (The MathWorks, Natick, Massachusetts) using an image-processing algorithm (13). The images were reconstructed using a de-aliasing technique similar to that used by Thomas et al. (14) and Rovner et al. (15).

The 1-dimensional, incompressible, Euler equation, shown in Equation 1, where P is the pressure, ρ is constant blood density, and v is velocity, s is position, and t is time, was used to calculate the relative pressures within the region of interest from the reconstructed velocity field. The pressure difference at each point along a scan line was measured relative to the position of the mitral annulus just before mitral valve opening by calculating the line integral between them (2,16,17). The first term of the right side of Equation 1 is the inertial component, and the second term is the convective component.

$$\frac{\partial P}{\partial s} = -\rho . \left(\frac{\partial v}{\partial t} + v . \frac{\partial v}{\partial s} \right) \quad [1]$$

From the temporal profile of the LV apex pressure relative to LA pressure, the peak IVPD from the mitral valvular annulus to the LV apex was calculated as previously described by Greenberg et al. (17) and Rovner et al. (15) (Fig. 1). This method has been validated by comparison to direct measurements with micromanometers (2,17). IVPD from the LA to mid-LV and IVPD from mid-LV (2 cm from the mitral annulus) to LV apex were also calculated (Fig. 1). IVPD values were measured from 3 beats, and the mean values were used for the final analysis.

Statistics. Numerical data were shown as mean and standard deviation unless otherwise mentioned. Numerical data were compared between diastolic functional grades by 1-way analysis of variance with Dunnett's post-hoc test using the normal group as reference, unless otherwise mentioned. Categorical data were compared with a chi-square method. Responses to dobutamine infusion by diastolic functional grades were compared using 2-way analysis of variance with repeated measure(s). Pearson correlation was performed to determine the association between the response of IVPD to the infusion of dobutamine and that of systolic mitral annular velocity (s′). A 2-tailed probability (p) value <0.05 was accepted as significant.

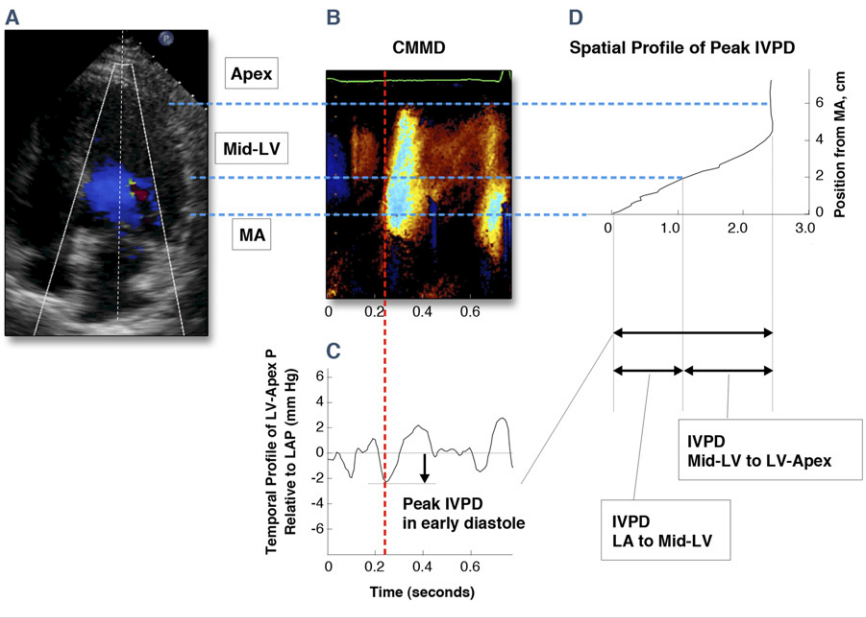

Figure 1. IVPD Measurement

(A) Four-chamber view showing mitral inflow; **(B)** corresponding color M-mode Doppler image; **(C)** temporal profile of LV apex pressure relative to LA pressure (LAP); **(D)** spatial profile of IVPD at peak negative IVPD from LA to LV apex. The **blue dotted line** shows corresponding positions of mitral annulus, mid-LV, and LV apex; the **red dashed line** shows the time of peak negative IVPD in early diastole. Color M-mode Doppler (CMMD) images **(B)** were recorded with the cursor parallel to mitral inflow in an apical 4-chamber view **(A)**. The 1-dimensional, incompressible, Euler equation, shown in Equation 1, was used to calculate the pressure gradients at each point. The pressure difference at each point along a scan line was measured relative to the position of the mitral annulus just prior to mitral valve opening by calculating the line integral between them. A temporal profile of LV apex pressure relative to LA pressure was generated, and the peak negative IVPD in early diastole was identified **(C)**. At the timing of the peak negative IVPD, the peak IVPD from the mitral valvular annulus to the LV apex and the IVPD from the LA to mid-LV and IVPD from mid-LV (2 cm from the mitral annulus) to LV apex were measured **(D)**. IVPD = left ventricular intraventricular pressure difference; LA = left atrium; LV = left ventricle; MA = mitral annulus.

Table 1. Clinical Characteristics

	Normal (n = 21)	Grade 1 (IR) (n = 14)	Grade 2 (PN) (n = 80)	Grade 3 (RF) (n = 51)	p Value*
Background					
Age, yrs	50 ± 11	64 ± 13†	61 ± 12†	64 ± 13†	<0.01
Male	14 (67)	10 (71)	40 (50)	22 (43)	0.13
End-stage renal disease	6 (29)	1 (7)	17 (21)	15 (29)	0.31
Heart failure	1 (5)	0 (0)	1 (1)	1 (2)	0.70
Hypertension	14 (67)	9 (64)	65 (81)	44 (86)	0.13
Diabetes mellitus	4 (19)	1 (7)	35 (44)	22 (43)	0.01
Dyslipidemia	11 (52)	6 (43)	42 (53)	29 (57)	0.83
Drugs					
CCB	6 (29)	3 (21)	23 (29)	22 (43)	0.25
BB	9 (43)	5 (36)	45 (56)	34 (67)	0.10
ACEI/ARB	8 (38)	6 (43)	38 (48)	26 (51)	0.78
Diuretics	5 (24)	3 (21)	30 (38)	18 (35)	0.49
Statin	11 (52)	5 (36)	39 (49)	25 (49)	0.79
Echocardiographic parameter					
Left atrial diameter, mm	36 ± 6	34 ± 4	37 ± 6	38 ± 5	0.11
Left ventricular mass, g	144 ± 50	144 ± 48	155 ± 47	180 ± 65†	0.02
Indication of dobutamine stress echocardiography					0.84
Screening	8 (38)	8 (57)	39 (49)	28 (55)	
Dyspnea	1 (5)	0 (0)	2 (3)	2 (4)	
Chest pain	11 (52)	6 (43)	36 (45)	21 (41)	
Other symptoms	1 (5)	0 (0)	3 (4)	0 (0)	
Maximum pharmacological stress					
Peak dobutamine dose, μg/kg/min	37 ± 6	39 ± 4	37 ± 6	36 ± 7	0.52
Atropine usage	15 (71)	7 (50)	49 (61)	31 (61)	0.64
Reason for termination					
End of protocol/THR	20 (95)	14 (100)	73 (91)	44 (86)	0.36
Any symptom/adverse event	1 (5)	0 (0)	7 (9)	7 (14)	

Values are mean ± SD or n (%). *Analysis of variance or chi-square test as appropriate; †$p < 0.05$ versus normal by Dunnett's post-hoc test.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CCB = calcium channel blocker; IR = impaired relaxation; PN = pseudonormal filling; RF = restrictive filling; THR = target heart rate.

RESULTS

Patient characteristics. We studied 166 consecutive patients undergoing stress echocardiography who had no inducible ischemia and a preserved EF. Twenty-one of the subjects had normal diastolic function, 14 impaired relaxation (grade 1), 80 pseudonormal filling (grade 2), and 51 restrictive filling (grade 3). Patient characteristics by diastolic functional grade are shown in Table 1.

Hemodynamic response. At rest, patients with diastolic dysfunction grades 2 and 3 had higher systolic blood pressures than the normal subjects (see Online Appendix B for additional information). Other hemodynamic variables were similar between normal subjects and those with diastolic dysfunction. LV dimensions were similar between patient groups at rest and during peak dobutamine infusion.

The chronotropic responses to the infusion of dobutamine were similar between the groups except that at peak dobutamine infusion, patients with grade 3 diastolic dysfunction achieved lower heart rates than normal subjects (see Online Appendix B for additional information). However, the ratios of the achieved heart rate to age-predicted maximum heart rate were similar between groups. All groups increased cardiac output to approximately 7 l/min from the resting value of approximately 4 l/min. This increase of cardiac output was predominantly due to increase in heart rate. Although the EF increased in all the groups, end-diastolic and end-systolic volumes both decreased, which resulted in a decrease in stroke volume. In all groups, systemic vascular resistance decreased; however, aortic compliance decreased, consistent with an increase in the pulsatile component of cardiac afterload. Total LV afterload, evaluated as effective aortic elastance, increased in all groups. These

Table 2. Doppler Echocardiographic Variables

	Normal		Grade 1 (IR)		Grade 2 (PN)		Grade 3 (RF)		
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	p Value*
E at rest, cm/s	21	89 ± 16	14	57 ± 10†	80	76 ± 15†	51	98 ± 21	<0.01
A at rest, cm/s	21	69 ± 18	14	66 ± 24	80	81 ± 18†	51	97 ± 24†	<0.01
E/A at rest	21	1.37 ± 0.44	14	0.94 ± 0.29†	80	0.98 ± 0.3†	51	1.08 ± 0.44†	<0.01
Deceleration time at rest, ms	20	221 ± 39	13	255 ± 74	79	241 ± 50	51	245 ± 56	0.25
e′ at rest, cm/s	21	10.9 ± 1.2	14	8.7 ± 1.3	80	7.2 ± 1.3†	51	6.1 ± 1.3†	<0.01
a′ at rest, cm/s	21	10.2 ± 1.9	14	11.4 ± 2.4	80	9.6 ± 1.9†	51	8.5 ± 2.2†	<0.01
s′, cm/s									<0.01‡
Rest	16	8.6 ± 1.4	11	9.0 ± 3.1	75	7.3 ± 1.2†	45	6.8 ± 1.1†	
Peak dose	16	15.2 ± 3.9	11	14.7 ± 2.3	75	12.1 ± 3.0†	45	10.4 ± 2.3†	
Δ (peak dose − at rest)	16	6.6 ± 3.7	11	5.7 ± 2.2	75	4.8 ± 2.8†	45	3.6 ± 2.1†	
E/e′ at rest	21	8.2 ± 1.6	14	6.6 ± 1.1	80	10.5 ± 1.3†	51	16.3 ± 3.3†	<0.01

*Analysis of variance (ANOVA); †p < 0.05 versus normal by Dunnett's post-hoc test; ‡ANOVA with 1 repeated measure.
a′ = late diastolic mitral annular velocity; e′ = early diastolic mitral annular velocity; s′ = systolic mitral annular velocity; other abbreviations as in Table 1.

hemodynamic responses were similar between normal subjects and those with diastolic dysfunction.

Doppler echocardiography. The e′ and s′ velocities were significantly correlated at rest ($r = 0.51$, $p < 0.0001$) (Table 2). During peak dobutamine infusion, s′ was augmented in all the groups. However, the magnitude of the augmentation of s′ was less in patients with diastolic function grades 2 and 3 than in normal subjects. We were unable to constantly measure e′ during stress because of fusion of the early diastolic mitral annular velocity (e′) and late diastolic mitral annular velocity (a′) waves.

IVPD responses to dobutamine infusion by diastolic functional grade. Patients with normal diastolic function had similar IVPD to patients with diastolic dysfunction at rest. All groups increased the IVPD in response to dobutamine (Table 3). However, at peak dobutamine, the patients with diastolic dysfunction had a smaller increase in the IVPD than patients with normal diastolic function (Table 3, Figs. 2 and 3). Both normal subjects and patients with diastolic dysfunction showed similar increases of IVPD from the LA to mid-LV in response to dobutamine (Fig. 3B). The difference in the total IVPD in the diastolic

Table 3. IVPD at Rest and During Dobutamine Infusion

	Normal		Grade 1 (IR)		Grade 2 (PN)		Grade 3 (RF)		
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	p Value*
Total IVPD									0.02
At rest	21	2.80 ± 1.07	14	2.12 ± 0.96	80	2.62 ± 1.08	51	3.15 ± 1.20	
Low dose	21	3.91 ± 2.21	14	2.61 ± 0.96†	80	3.92 ± 1.6	51	4.07 ± 1.48	
Peak dose	21	5.00 ± 1.74	14	2.85 ± 1.03†	80	3.66 ± 1.48†	51	4.23 ± 1.59	
Δ (peak dose − at rest)	21	2.20 ± 1.95	14	0.73 ± 1.33†	80	1.04 ± 1.63†	51	1.08 ± 1.57†	
IVPD from LA to mid-LV									0.11
At rest	21	1.58 ± 0.59	14	1.09 ± 0.39	80	1.49 ± 0.57	51	1.86 ± 0.84	
Low dose	21	2.12 ± 0.99	14	1.24 ± 0.38†	80	1.87 ± 0.72	51	2.16 ± 0.88	
Peak dose	21	2.29 ± 0.89	14	1.79 ± 0.64	80	1.80 ± 0.71†	51	2.37 ± 0.96	
Δ (peak dose − at rest)	21	0.71 ± 0.82	14	0.70 ± 0.84	80	0.31 ± 0.77	51	0.51 ± 1.13	
IVPD from mid-LV to LV apex									<0.01
At rest	21	1.40 ± 0.80	14	1.27 ± 0.64	80	1.35 ± 0.76	51	1.52 ± 0.72	
Low dose	21	2.05 ± 1.47	14	1.55 ± 0.79	80	2.27 ± 1.26	51	2.08 ± 0.95	
Peak dose	21	3.12 ± 1.24	14	1.41 ± 0.59†	80	2.19 ± 1.04†	51	2.14 ± 1.29†	
Δ (peak dose − at rest)	21	1.73 ± 1.29	14	0.15 ± 0.72†	80	0.84 ± 1.12†	51	0.63 ± 1.32†	

*Analysis of variance with repeated measures; †p < 0.05 versus normal by Dunnett's post-hoc test.
IVPD = intraventricular pressure difference; LA = left atrium; LV = left ventricle; other abbreviations as in Table 1.

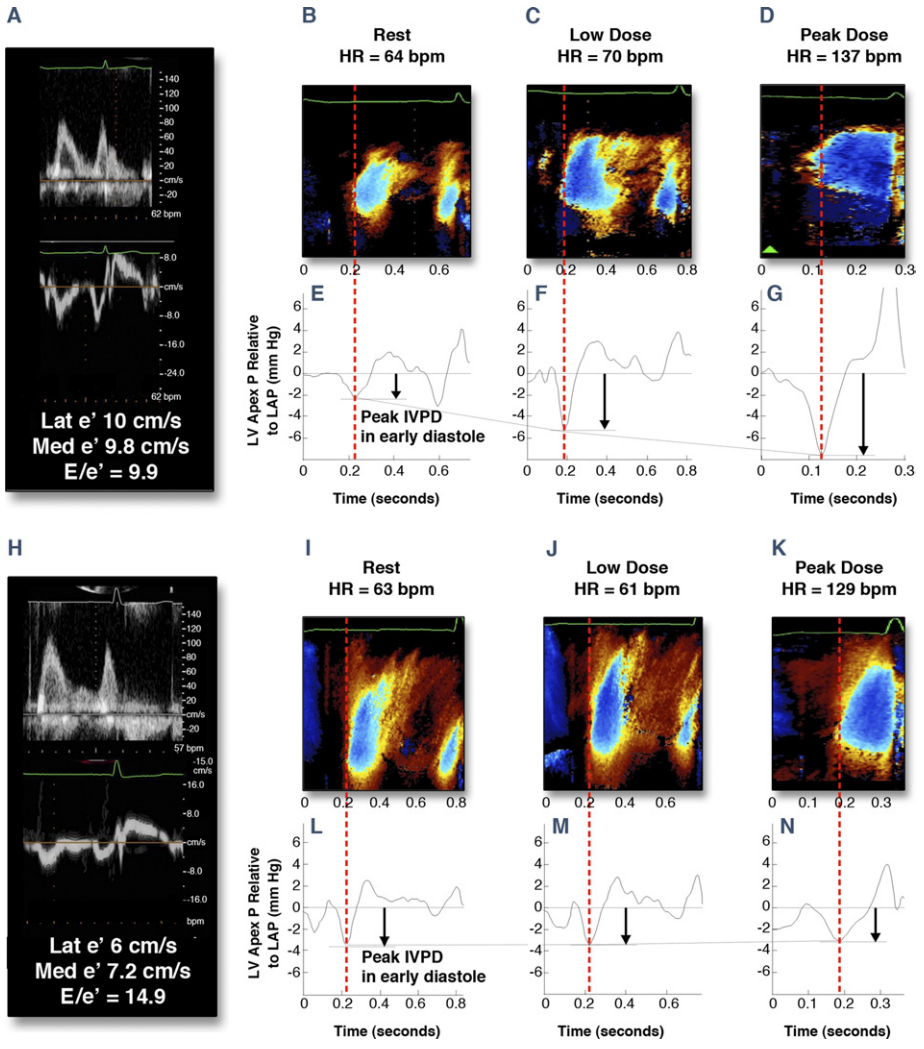

Figure 2. Examples of IVPD During Dobutamine Stress Echocardiography

(A to G) Images from a subject with normal diastolic function, 54-year-old male, and an EF of 54%; **(H to N)** images from a subject with pseudonormal filling pattern, 69-year-old female, and an EF of 63%. **(A and B)** Transmitral inflow Doppler image and corresponding tissue Doppler image at septal mitral annulus; **(B, C, D, I, J, and K)** color Doppler images; **(E, F, G, L, M, and N)** temporal profile images of IVPD; **(B, E, I, and L)** images at rest; **(C, F, J, and M)** images during low-dose dobutamine infusion; and **(D, G, K, and N)** images during peak-dose dobutamine infusion. **Red dashed line** shows the timing of peak negative IVPD in early diastole; the **dotted line** shows the change of peak IVPD in response to the infusion of dobutamine. The patients with diastolic dysfunction had a smaller increase in the IVPD than patients with normal diastolic function in response to the infusion of dobutamine. bpm = beats/min; e′ = early diastolic mitral annular velocity; EF = ejection fraction; HR = heart rate; other abbreviations as in Figure 1.

dysfunction group was due to less augmentation of the IVPD from mid-LV to the apex in response to the peak-dose infusion of dobutamine (Fig. 3C). The results were similar in the patients who had not been receiving beta-blockers (Online Appendix C). Results were also similarly analyzed by tertiles of e′ (Online Appendix D). There was reduced dobutamine augmentation of the mid-LV to apex IVPD in the patients with e′ <6.5 cm/s.

This difference in the response of IVPD between normal and diastolic dysfunction was predominantly due to reduced adrenergic augmentation of the inertial acceleration with the peak-dose infusion of dobutamine, whereas convective deceleration was not different between groups (Fig. 4).

The change of IVPD in response to the infusion of dobutamine significantly correlated with the change of s′ to dobutamine (Fig. 5).

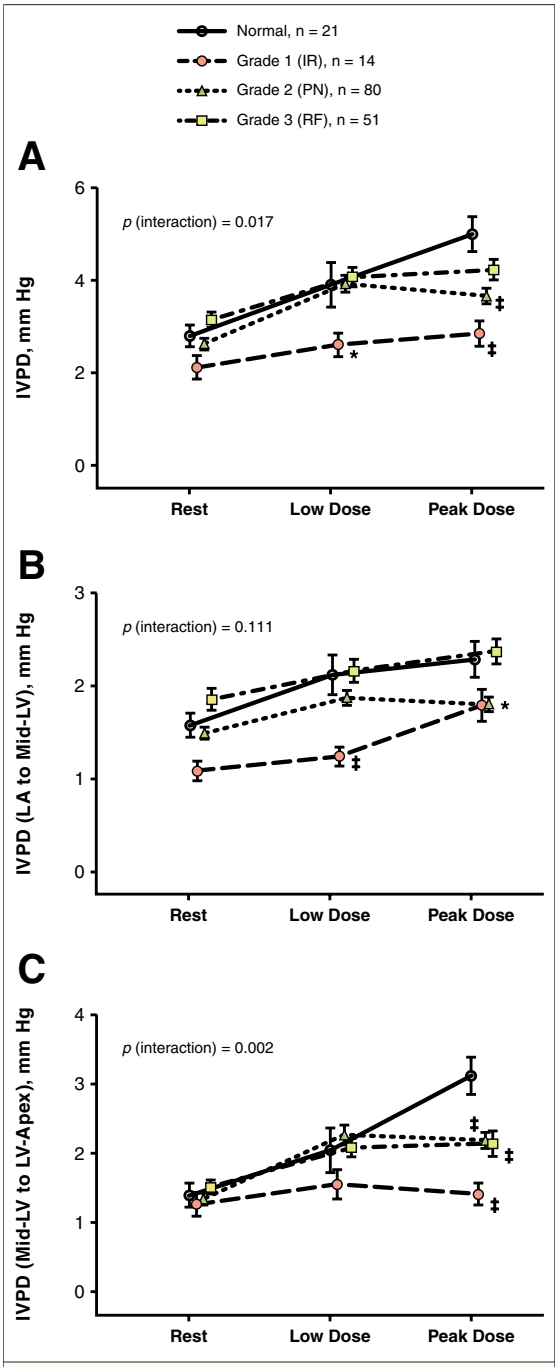

Figure 3. IVPD Responses to Dobutamine Infusion by Diastolic Functional Grades

(A) IVPD; **(B)** IVPD from LA to mid-LV; **(C)** IVPD from mid-LV to LV apex. *p < 0.05 versus normal; †p < 0.01 versus normal; ‡p < 0.001 versus normal. IR = impaired relaxation; PN = pseudonormal filling; RF = restrictive filling; other abbreviations as in Figures 1 and 2.

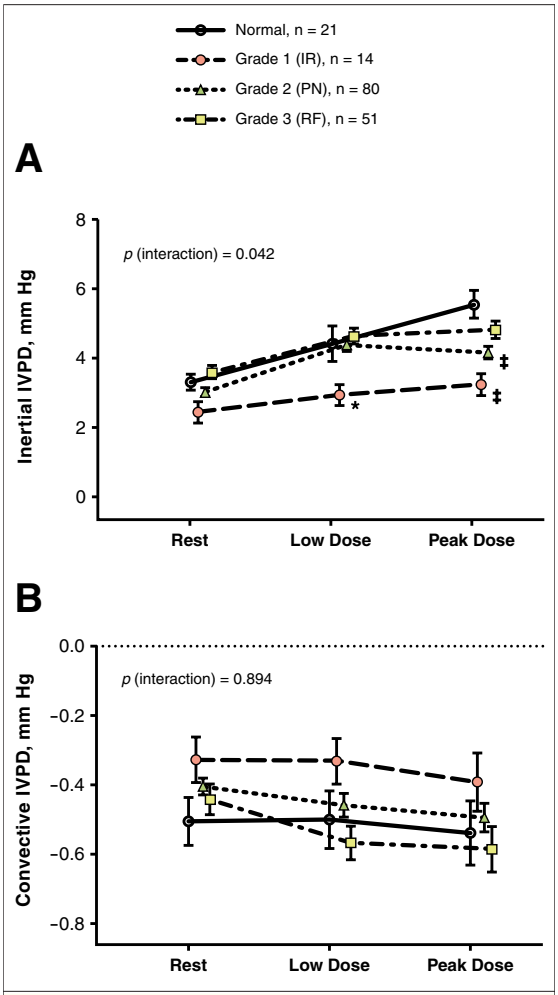

Figure 4. Responses to Dobutamine Infusion by Inertial Acceleration and Convective Deceleration of IVPD

(A) Inertial IVPD; **(B)** convective IVPD. *p < 0.05 versus normal; †p < 0.01 versus normal; ‡p < 0.001 versus normal. Abbreviations as in Figures 1 and 3.

DISCUSSION

In early diastole, the rapid relaxation of the LV generates a progressive pressure difference from the LA to the LV apex, resulting in rapid early diastolic filling. This IVPD is considered a manifestation of LV suction (18–20). The IVPD can now be noninvasively calculated using the data obtained with CMMD to integrate the Euler equation (2,16,17). The pressure difference is generated by inertial acceleration driven by the recoil of elastic elements compressed during ejection and is reduced by convective deceleration (2,21,22). The reduction of IVPD in patients with reduced EF is due to both reduced inertial acceleration and increased convective deceleration resulting from flow into a dilated ventricle (2). Parker et al. (23) found that enhanced LV relaxation with dobutamine measured using the time constant was preserved in patients with HF and reduced EF. However, Yotti et al. (2) found a

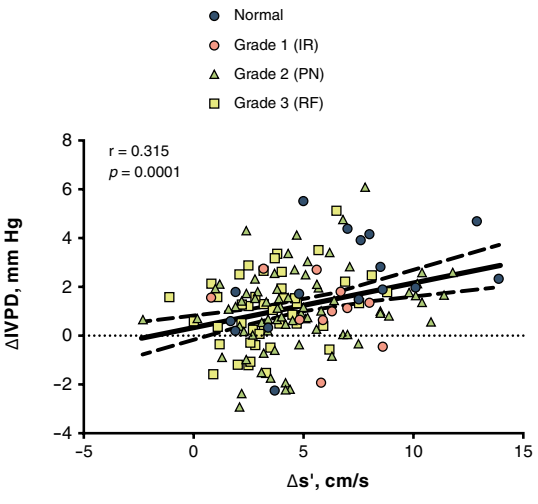

Figure 5. Correlation Between Δs′ and ΔIVPD

IVPD = left ventricular intraventricular pressure difference; s′ = systolic mitral annular velocity; other abbreviations as in Figures 1 and 3.

blunted response to adrenergic stimulation of the IVPD in the patients with HF and reduced EF. Our study found that subjects with diastolic dysfunction and a preserved EF have a reduced adrenergic augmentation of the IVPD between the LA and LV apex, predominantly due to reduced inertial acceleration between the mid-LV and LV apex (Fig. 3).

The IVPD can be increased due to a fall in LV diastolic pressures or increase in LA pressure. Alterations in LA pressure impact the IVPD between the LA and the inflow tract, whereas LV suction produces a progressive IVPD, thus the pressure difference between mid-LV to LV apex differentiates LV filling resulting from LV suction and filling predominately due to an increase in LA pressure (13,18,19,24). Our observation of reduced dobutamine augmentation of the IVPD from mid-LV to LV apex in patients with diastolic dysfunction is consistent with diminished adrenergic augmentation of LV suction and may contribute to exercise intolerance in this patient population (25).

Borlaug et al. (10) found exercise-induced pulmonary hypertension and elevation of pulmonary capillary wedge pressure in patients with exertional dyspnea with preserved EF. Impaired augmentation of the early IVPD in subjects with diastolic dysfunction may help explain this observation (26).

Many factors other than diastolic function, including an impaired arterial vasodilation may contribute to exercise intolerance in HF with a preserved EF (HFpEF) (26,27). However, we observed that vascular responses to adrenergic stimulation were similar between groups (Online Appendix B), consistent with other observations (28).

Patients with grade 1 diastolic LV dysfunction showed the lowest IVPD compared with grades 2 and 3 diastolic dysfunction. This was due to a higher IVPD from the LA to mid-LV in the patients with grades 2 and 3 diastolic dysfunction than in patients with grade 1 diastolic dysfunction, suggesting that LA pressure was higher in these patients. Interestingly, patients with grade 1 diastolic dysfunction had the smallest augmentation. With grade 1 diastolic dysfunction, the reduced adrenergic response was predominately due to reduced inertial acceleration, whereas with more severe diastolic dysfunction, it was predominately due to greater convective deceleration.

During ejection, the mitral annulus is pulled toward the LV apex. The velocity of this motion (s′) is a measure of LV contractility. Normally, early in diastole, the mitral annulus recoils, moving rapidly away from the apex into the LA (29). This is apparent on tissue Doppler as e′ and may contribute to the generation of the early diastolic IVPD. Despite having normal EFs, we found that both s′ and e′ were reduced at baseline in patients with diastolic dysfunction. At rest, e′ and s′ were significantly correlated ($r = 0.51$, $p < 0.0001$). Although we could not reliably assess e′ at peak dobutamine due to fusion of e′ and a′, there was a reduction of the response of s′ to dobutamine in patients with diastolic dysfunction. Others have observed that patients with HFpEF have impaired augmentation of s′ and e′ in response to a low dose of dobutamine (30) and is related to the 6-min walk distance (31). These data suggest that a failure of augmentation of longitudinal contraction and lengthening in response to adrenergic stimulation contributes to the reduced response of the IVPD in patients with diastolic dysfunction.

Increased heart rate contributes to the normal response to adrenergic stimulation through the force-frequency and relaxation-frequency relation (32,33), which may be preserved in patients with HFpEF (34,35). When the patients in our study did not achieve their target heart rate, atropine was used, which potentially confounded the results. However, the portion receiving atropine was similar in the groups with and without diastolic dysfunction. Although some reported that there is chronotropic incompetence in patients with HFpEF

(27,36), we did not observe the difference between diastolic dysfunction subgroups in response to adrenergic stimulation.

The use of beta-blockers may potentially influence our results. The patients with advanced diastolic dysfunction in our study were more likely to be receiving beta-blockers (Table 1), although the use did not reach statistical difference. In addition, we stopped the beta-blocker on the day of examination, and we used high doses of dobutamine, which overcomes the effect of beta-blockade. Furthermore, limiting our analysis to the patients who were not receiving beta-blockers produced similar results.

We classified the patients' diastolic dysfunction using e′ and E/e′. A more comprehensive evaluation of diastolic function, including E deceleration time, LA volume, pulmonary venous flow, response to the Valsalva maneuver, and other measures, might have produced a more accurate classification of our patients.

CONCLUSIONS

Patients with diastolic dysfunction and a normal EF have reduced adrenergic augmentation of the IVPD from the mid-LV to the apex. This is consistent with reduced apical suction and may contribute to exercise intolerance.

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Key Words: color M-mode Doppler ■ diastolic dysfunction ■ dobutamine stress echocardiography ■ intraventricular pressure difference.

▶APPENDIX

For supplemental information, please see the online version of this article.