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Impaired Left Ventricular Stroke Volume Reserve During Clinical Dobutamine Stress Predicts Future Episodes of Pulmonary Edema

Charaslak Charoenpanichkit, MD,* William C. Little, MD,* Sangeeta Mandapaka, MD,* Erica Dall'Armellina, MD,* Timothy M. Morgan, PHD,† Craig A. Hamilton, PHD,‡ W. Gregory Hundley, MD*§

Winston-Salem, North Carolina

Objectives The purpose of this study was to determine whether dobutamine-induced abnormal stress changes in left ventricular stroke volume (LVSV) and aortic stiffness predict future pulmonary edema.

Background Increased aortic stiffness that decreases LVSV during adrenergic stress may serve as a marker for future pulmonary edema (PE).

Methods We measured LVSV, ventriculovascular stiffness (pulse pressure/$LVSV_{index}$), and aortic distensibility at rest and during intravenous dobutamine administration using cardiovascular magnetic resonance. Personnel blinded to dobutamine cardiovascular magnetic resonance followed participants longitudinally over time to identify those admitted to the hospital with PE. Data for 44 participants who had a hospital admission for PE were compared with data for 72 participants of similar age, sex, and resting left ventricular ejection fraction who remained PE free.

Results Expressed as median and interquartile range, participants with and without PE exhibited a decreased stress/rest LVSV ratio (0.9 [range 0.7 to 1.1] vs. 1.0 [range 0.9 to 1.2], respectively; $p = 0.002$), an increased ventriculovascular stiffness stress/rest ratio (1.4 [range 1.0 to 1.6] vs. 1.0 [range 0.8 to 1.3], respectively; $p \leq 0.001$); and a decreased stress-induced measure of aortic distensibility (0.8 mm Hg^{-3} [range 0.3 to 1.3 mm Hg^{-3}] vs. 1.6 mm Hg^{-3} [range 1.2 to 3.2 mm Hg^{-3}], respectively; $p = 0.002$). After accounting for age, sex, left ventricular ejection fraction, risk factors for PE, and the presence of dobutamine-induced ischemia, LVSV reserve and the stress/rest ventriculovascular stiffness ratio still differed ($p < 0.008$ for both) in those with and without PE.

Conclusions In patients without inducible ischemia during dobutamine stress testing in whom one might otherwise assume a favorable prognosis, the failure to increase LVSV or an increase in ventriculovascular stiffness indicates patients at risk of subsequent PE. (J Am Coll Cardiol 2011;57:839–48) © 2011 by the American College of Cardiology Foundation

Acute myocardial ischemia or myocardial infarction (MI) may limit the ability of the left ventricle to augment its stroke volume in response to stress (1). In this situation, the right ventricle may displace blood into the lungs, increase left atrial pressure, and produce pulmonary edema (PE) (2,3). The onset of PE (often accompanied by arterial hypertension) can occur in the absence of a decrease in left ventricular ejection fraction (LVEF) or with the development of new regional wall motion abnormalities (4). As shown by Kawaguchi et al. (5), increased vascular stiffness can adversely affect left ventricular (LV) performance in patients with PE who do not exhibit myocardial ischemia (5).

Accordingly, we hypothesized that in the absence of ischemia, an inability of the left ventricle to increase stroke volume due to an abnormal increase in arterial stiffness may predispose patients to the future development of PE. To evaluate this hypothesis, we measured stress/rest left ventricular stroke volume (LVSV), ventriculovascular stiffness (pulse pressure [PP]/LVSV index [$LVSV_i$] for body surface area), and aortic distensibility during administration of

From the *Department of Internal Medicine (Cardiology Section), Wake Forest University School of Medicine, Winston-Salem, North Carolina; †Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina; ‡Department of Biomedical Engineering, Wake Forest University School of Medicine, Winston-Salem, North Carolina; and §Department of Radiology, Wake Forest University School of Medicine, Winston-Salem, North Carolina. Research supported in part by the following grants from the National Institutes of Health: R01 HL076438, R33 CA1219601, T32HL091824, P30AG21332, and MO1-RR07122. Dr. Little has served as a consultant to CorAssist Cardiovascular Ltd., Celladon Corporation, Boston Scientific, Medtronic, Bio-Control Medical, CVRx, Amylin Pharmaceuticals, and Gilead. All other authors have reported that they have no relationships to disclose.

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Abbreviations and Acronyms

DCMR = dobutamine cardiovascular magnetic resonance
LV = left ventricular
LVEDV = left ventricular end-diastolic volume
LVSV = left ventricular stroke volume
$LVSV_i$ = left ventricular stroke volume index
MI = myocardial infarction
PE = pulmonary edema
PP = pulse pressure
SBP = systolic blood pressure

intravenous dobutamine in patients in whom PE subsequently developed. We compared their data with data for a group of individuals who also underwent dobutamine stress testing but in whom PE did not develop. Stratified analyses were performed to address the association of LVSV with future PE in participants with and without dobutamine-induced LV wall motion abnormalities indicative of ischemia.

Methods

Study design and population. The Institutional Review Board of the Wake Forest University School of Medicine approved the study, including the review of medical records. In addition, study participants provided informed consent for the dobutamine stress imaging procedure and post-testing analysis of the imaging data. We used a study design in which participants experiencing PE were selected from a patient population that previously (>1 month) had undergone dobutamine cardiovascular magnetic resonance (DCMR) stress testing. From 362 DCMR stress examinations that were consecutively performed between April 1997 and April 2003, we identified all 44 individuals who subsequently were hospitalized for PE over a 6-year follow-up period at our medical center. PE was defined as an acute onset of dyspnea in the presence of rales on physical examination recorded by the managing physician, evidence of pulmonary congestion on the chest radiograph, and subsequent receipt of intravenous diuretic therapy to relieve pulmonary congestion. This definition was commensurate with selection of criteria used to adjudicate PE due to heart failure in the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) study (6). Patients with lung cancer or moderate to severe valvular heart diseases were excluded from analyses. Our comparison population was selected from the same 362 individuals who had undergone a DCMR stress examination and in whom future PE did not develop in the same follow-up time frame (Fig. 1). Blinded to the cardiac and vascular imaging study results, subjects in the control group were selected to have a distribution of sex, age, and resting LVEF similar to that of the 44 individuals who experienced PE.

Personnel performing analyses were blinded to other aspects of the study. For example, those unaware of stress testing results reviewed the medical charts to identify PE outcomes of the participants. Likewise, those assessing DCMR stress data were blinded to participant outcomes.

Dobutamine/atropine cardiac magnetic resonance protocol. Images were acquired with a 1.5-T Horizon (General Electric Medical Systems, Milwaukee, Wisconsin) whole-body imaging system using a phased-array cardiac surface coil according to previously published techniques (7,8).

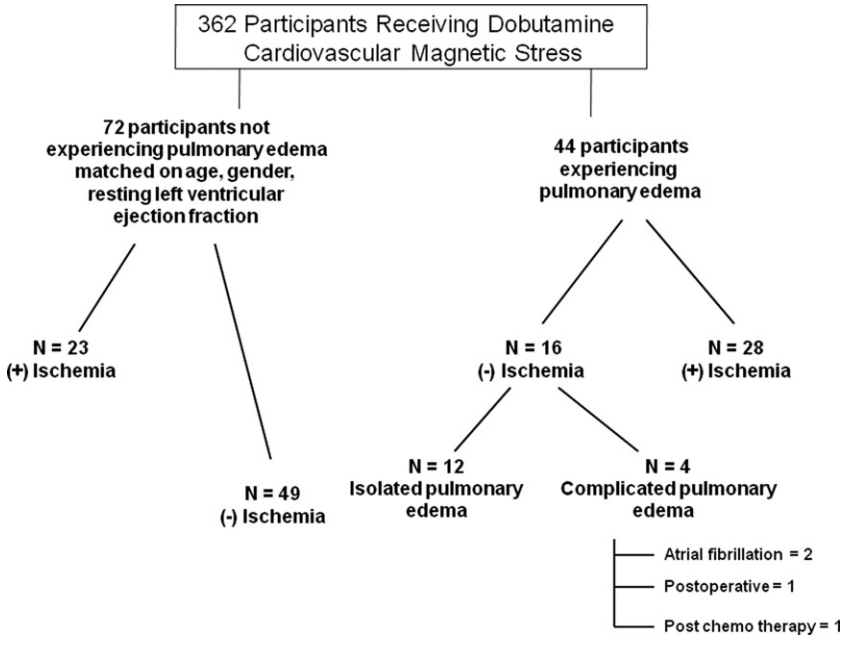

Figure 1 Study Population

Diagram segregating participants receiving dobutamine cardiac magnetic resonance stress testing in whom pulmonary edema developed (n = 44) and an age,- sex-, and resting left ventricular ejection fraction–matched distribution of participants (n = 72) in whom pulmonary edema did not develop.

Dobutamine was infused incrementally from low dose (7.5 mcg/kg/min) to high dose (20 to 40 mcg/kg/min), and atropine was infused (up to 1.5 mg) to achieve 85% of the maximum predicted heart rate response for age, the heart rate response associated with a maximal test (7,8). Images were acquired at rest, at low- and high-dose infusion, and then after 10 min of recovery (7,8). K-space segmentation was adjusted to achieve a temporal resolution of 20 ms for determining LV end-systolic dimensions at peak stress.

Image analysis. LV volumes were determined according to previously published techniques using a biplane area-length technique (8–10) from the 4- and 2-chamber views of the left ventricle. Cardiovascular stiffness was assessed using previously published methods using measurements of aortic distensibility (11) and the brachial PP/LVSV$_i$ (12). Aortic distensibility was defined as the maximum aortic area − the minimum aortic area ÷ minimum aortic area × brachial PP (13,14).

Statistical analysis. Categorized data were summarized by percentages. Because many of the continuous data were skewed, the central value and spread of the distribution of values are presented as the median and interquartile range (IQR). When box-and-whisker plots were given, the box demonstrated the 25th, 50th, and 75th percentiles, and the whiskers represented the largest values within 1.5 times the interquartile range from the median. Comparison of proportions between groups was tested for significance using the Fisher exact test.

The association between measures was estimated and tested using Spearman's rank correlation. Comparison of continuous data between groups was tested for significance using the Wilcoxon rank sum test. Comparisons of change in measures during the stress test were tested for significance using the Wilcoxon rank test for paired comparisons. Analysis of covariance, in which other factors are included in the model, was conducted using rank-based nonparametric methods. The estimates and tests of the association of increased risk of PE by DCMR data were estimated and tested for significance using Cox's proportional hazards model for case-control studies (15). The estimate of group effect was made after controlling for known risk factors of PE (age, sex, diabetes, hypertension, previous coronary artery revascularization or MI, body mass index). The statistical comparisons were 2 tailed, and p values <0.05 were considered statistically significant.

Results

The average follow-up times for those with and without future PE were similar (6 ± 2 years and 6 ± 2 years, respectively; p = 0.41). Isolated PE occurred in 29 cases; in other cases, PE occurred along with MI (n = 4), acute renal failure (n = 3), post-operatively (n = 3), during atrial fibrillation with a rapid ventricular response (n = 3), after chemotherapy (n = 1), and after cardiac arrest (n = 1). As shown in Figure 1, we performed analyses on our entire study population and additional stratified analyses on only those with isolated PE.

Demographic data of the study participants are shown in Table 1. The age and sex of both the participant groups were similar. Patients with future PE exhibited more diabetes, but the prevalence of hypertension, a history of MI, hypercholesterolemia, smoking, and medication use were similar between the groups. Body mass index trended higher in the PE participants.

Hemodynamic data from the subjects' dobutamine studies are also shown in Table 1. Those with future PE received 20 μg/kg/min (IQR: 20 to 30 μg/kg/min) dobutamine and 0 mg (IQR: 0.0 to 0.3 mg) atropine, and those without future PE received 20 μg/kg/min (IQR: 20 to 30 μg/kg/min) dobutamine and 0 mg (IQR: 0.0 to 0.3 mg) atropine during testing (p = 0.51 and 0.64, respectively). Participants without future PE exhibited higher peak stress heart rate responses than those with PE (p = 0.02).

LV volumes, LVEF, cardiac output, and vascular stiffness data are shown in Table 2. Patients with PE had a higher prevalence of dobutamine-induced LV wall motion abnormalities indicative of ischemia (63% vs. 32%, p = 0.001). Rest measures of LV volumes, LVEF, and ventriculovascular stiffness were similar in both groups. At peak stress, left ventricular end-diastolic volume (LVEDV) was similar in those with and without PE (101 ml [range 79 to 154 ml] vs. 104 ml [range 73 to 122 ml], p = 0.29), the LV end-systolic volume was lower in those without versus those with PE (41 ml [range 29 to 61 ml] vs. 58 ml [range 43 to 97 ml], respectively; p = 0.007). Those without versus those with PE exhibited higher LVSV reserve measurements (1.0 [range 0.9 to 1.5] vs. 0.9 [range 0.7 to 1.0], respectively, p = 0.002) (Fig. 2). After adjustment for age, sex, diabetes, hypertension, previous coronary artery revascularization, body mass index, and previous MI, LVSV reserve (stress/rest LVSV) still differed in those with and without future PE (p = 0.002). Participants with an LVSV reserve of <1.0 were 50% more likely to experience PE ($p < 0.001$) than those with an LVSV reserve ≥ 1.0.

Measures of total vascular stiffness (PP/LVSV$_i$) were similar between the groups at rest. At peak stress, those with PE exhibited an increased PP/LVSV$_i$ (2.8 [range 2.2 to 4.3] vs. 2.5 [range 1.9 to 3.3], respectively; p = 0.04), and stress/rest ratios of PP/LVSV$_i$ (1.4 [range 1.0 to 1.6] vs. 1.0 [range 0.8 to 1.3], respectively; p = 0.001). As shown in Table 2 and Figure 2B, the stress/rest ratios of PP/LVSV$_i$ were higher, whereas stress-induced aortic distensibility was lower in participants with versus those without future PE.

Stratified analyses were performed in participants without inducible LV ischemia during dobutamine stress testing. As displayed in Figure 1 and Table 3, there were 12 subjects with isolated PE and no ischemia during dobutamine-induced stress. These 12 subjects were compared with the 49 subjects without PE who also had no inducible ischemia during dobutamine-induced stress. In these analyses, those with versus those without PE exhibited impaired LVSV

Table 1 Baseline Characteristic of Participants With and Without Pulmonary Edema

	All (n = 116)	Pulmonary Edema		p Value
		Yes (n = 44)	No (n = 72)	
Demographics				
Age, yrs	67 (60–74)	68 (60–76)	67 (59–73)	0.60
Sex, male	54	52	55	0.85
Body mass index, kg/m^2	29 (26–34)	30 (27–35)	29 (25–32)	0.13
Historical data				
Previous myocardial infarction	42	48	39	0.44
Hypertension	72	70	72	0.84
Diabetes mellitus	36	48	29	0.05
Hypercholesterolemia	57	59	55	0.85
Smoking	41	48	36	0.25
Medications				
Beta-blocker	40	39	42	0.85
Calcium-channel blocker	30	36	26	0.30
Nitrate	28	36	22	0.14
ACE inhibitor/ARB	37	43	33	0.33
Statin	30	32	43	0.83
Resting pulse pressure, mm Hg	63 (50–74)	62 (47–77)	63 (51–74)	0.52
Resting heart rate, beats/min	72 (64–81)	69 (64–82)	74 (65–81)	0.49
Resting SBP, mm Hg	137 (124–154)	134(121–153)	139 (126–159)	0.37
Resting DBP, mm Hg	76 (66–86)	74 (65–84)	76 (66–87)	0.25
Stress pulse pressure, mm Hg	71 (56–88)	70 (54–88)	71 (59–86)	0.66
Stress heart rate, beats/min	130 (119–135)	125 (105–131)	130 (120–135)	0.02
% MPHR	85 (79–87)	84 (67–86)	85 (81–88)	0.01
Stress SBP, mm Hg	144 (126–168)	143 (128–168)	144 (126–169)	0.91
Stress DBP, mm Hg	73 (65–85)	70 (63–81)	74 (65–86)	0.18
Stress/resting pulse pressure	10 (6–21)	12 (2–23)	5 (8–19)	0.08
Dobutamine, mcg/kg/min	20 (20–30)	20 (20–30)	20 (20–30)	0.51
Atropine, mg	0 (0–0.4)	0 (0–0.4)	0 (0–0.3)	0.64

Values are expressed as median (interquartile range) or %.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; DBP = diastolic blood pressure; MPHR = maximum predicted heart rate response for age; SBP = systolic blood pressure.

reserve (p = 0.02) (Fig. 3A) and a decrease in stress-induced aortic distensibility (p = 0.01) (Fig. 3B). Importantly, after adjustment for demographic and historical comorbidities associated with the future risk of PE, stress/rest ratios of LVSV reserve (p = 0.03), cardiovascular stiffness (p = 0.02), and stress aortic distensibility (p = 0.05) remained significantly different in those with versus those without PE.

Because we wanted to identify associations of our DCMR measures with PE in individuals with a preserved LVEF (often termed heart failure and preserved LVEF), we performed additional stratified analyses on the 59 participants with an LVEF ≥50% and found that the 18 participants with PE exhibited a lower LVSV reserve (0.9 [range 0.7 to 0.9] vs. 1.0 [range 0.9 to 1.1], p = 0.001), a higher stress/rest ratio of PP/LVSV (1.4 [range 1.0 to 1.7] vs. 1.1 [range 0.8 to 1.3], p = 0.02), and a trend toward a lower stress-induced aortic distensibility (0.8 [range 0.3 to 0.9] vs. 1.3 [range 0.8 to 2.7], p = 0.08) than the 41 individuals without future PE. Sixteen participants with an LVEF ≥50% exhibited inducible LV wall motion abnormalities indicative of ischemia. When we analyzed only the participants with an LVEF ≥50% and no inducible LV wall motion abnormalities indicative of ischemia, the results demonstrated that LVSV reserve and stress/rest ratios of PP/LVSV stiffness remained different in those with and without future PE (p = 0.02 and 0.04, respectively).

Overall, LVEDV decreased by 10 ml (range 1 to 19 ml) from rest to peak stress (p < 0.001) with a 12-ml (range 1 to 20 ml) versus 7-ml (range 1 to 16 ml) decrease in those without versus those with PE, respectively (p = 0.20). There was a small correlation of 0.30 (p = 0.001) between LVSV reserve and change in LVEDV. Systolic blood pressure (SBP) and PP increased 8 mm Hg (range −8 to 23 mm Hg) and 10 mm Hg (−6 to 21 mm Hg), respectively (p ≤ 0.001 for both) for all participants, with 61% of the participants having an increase in their SBP during the stress test. For the participants without versus those with PE, SBP increased by 5 mm Hg (range −10 to 22 mm Hg) and 14 mm Hg (range −1 to 23 mm Hg), respectively (p = 0.19 for the difference), and PP increased by 4 mm Hg (range −8 to 19 mm Hg) and 12 mm Hg (range 1 to 23 mm Hg), respectively (p = 0.08 for the difference). For those without ischemia during testing, SBP increased in subjects without versus those with PE by −1 mm Hg (range −10 to 14 mm Hg) and 9 mm Hg (range 1 to 21 mm Hg), respectively (p = 0.12 for the difference) in

Table 2 DCMR Findings in Participants With and Without Pulmonary Edema

		Pulmonary Edema		
	All (n = 116)	Yes (n = 44)	No (n = 2)	p Value
Resting EF	50 (40 to 55)	48 (36 to 54)	52 (44 to 55)	0.08
Resting EDV	110 (91 to 147)	116 (89 to 179)	109 (91 to 131)	0.43
Resting ESV	59 (43 to 83)	66 (42 to 114)	57 (43 to 72)	0.38
Resting SV	52 (41 to 63)	54 (37 to 72)	51 (44 to 58)	0.61
Stress EDV	103 (76 to 134)	101 (79 to 154)	104 (73 to 122)	0.29
Stress ESV	46 (31 to 75)	58 (43 to 97)	41 (29 to 61)	0.007
Stress SV	54 (41 to 62)	47 (34 to 58)	55 (48 to 65)	0.02
Resting EDVi	55 (45 to 73)	57 (43 to 87)	54 (46 to 70)	0.68
Resting ESVi	29 (16 to 35)	31 (21 to 54)	29 (23 to 38)	0.56
Resting SVi	26 (21 to 32)	27 (19 to 34)	25 (21 to 31)	0.77
Stress EDVi	52 (40 to 65)	53 (40 to 78)	52 (40 to 61)	0.41
Stress ESVi	24 (16 to 35)	26 (21 to 48)	22 (15 to 32)	0.02
Stress SVi	26 (21 to 32)	23 (17 to 31)	27 (24 to 33)	0.02
Resting PP/SV	1.2 (0.9 to 1.7)	1.1 (0.8 to 1.8)	1.2 (0.9 to 1.5)	0.56
Resting PP/SVi	2.5 (1.8 to 3.2)	2.3 (1.7 to 3.5)	2.5 (1.9 to 3.0)	0.63
Stress PP/SV	1.3 (1.0 to 1.7)	1.5 (1.1 to 2.3)	1.3 (1.0 to 1.6)	0.04
Stress PP/SVi	2.6 (2.0 to 3.7)	2.8 (2.2 to 4.3)	2.5 (1.9 to 3.3)	0.04
Stress/resting SV	0.6 (−6.5 to 6.7)	−3.7 (−12.5 to 2.5)	1.5 (−5.2 to 8.9)	0.002
Stress/resting SVi	0.3 (−3.3 to 3.4)	−2.1 (−6.0 to 1.3)	0.7 (−2.7 to 4.2)	0.002
Stress-resting PP/SV	0.1 (−0.2 to 0.5)	0.3 (−0.0 to 0.8)	−0.0 (−0.2 to 0.3)	<0.001
Stress/resting PP/SVi	0.2 (−0.4 to 0.9)	0.6 (−0.0 to 1.4)	−0.0 (−0.5 to 0.6)	<0.001
Stress/resting PP/SV	1.1 (0.8 to 1.5)	1.4 (1.0 to 1.6)	1.0 (0.8 to 1.3)	<0.001
Rest CO	3.6 (3.0 to 4.8)	3.7 (2.5 to 5.1)	3.6 (3.0 to 4.6)	0.69
Stress CO	6.7 (4.9 to 7.7)	5.3 (4.1 to 7.2)	7.0 (5.9 to 7.8)	0.002
Stress/resting CO	1.7 (1.4 to 2.1)	1.4 (1.2 to 1.8)	1.9 (1.5 to 2.2)	<0.001
Resting CI	1.8 (1.5 to 2.4)	1.9 (1.5 to 2.5)	1.8 (1.4 to 2.4)	0.89
Stress CI	3.2 (2.6 to 3.9)	2.8 (2.0 to 3.7)	3.4 (2.8 to 4.1)	0.001
Stress-rest CO	2.6 (1.9 to 3.9)	1.6 (0.9 to 2.9)	3.0 (2.2 to 4.2)	<0.001
Stress-rest CI	1.3 (0.7 to 1.9)	0.7 (0.4 to 1.4)	1.5 (1.1 to 2.1)	<0.001

Values are expressed as median (interquartile range).

CI = cardiac index; CO = cardiac output; DCMR = dobutamine cardiovascular magnetic resonance; EDV = end-diastolic volume; EDVi = end-diastolic volume index; EF = ejection fraction; ESV = end-systolic volume; ESVi = end-systolic volume index; PP/SV = pulse pressure/stroke volume; PP/SVi = pulse pressure/stroke volume index; SV = stroke volume; SVi = stroke volume index.

those without versus those with future PE. Similarly, PP increased by 3 mm Hg (range −10 to 16 mm Hg) and 10 mm Hg (range 1 to 25 mm Hg), respectively ($p = 0.05$ for the difference) in those without versus those with future PE.

Discussion

The results of this study indicate that 1) impaired augmentation of LVSV during dobutamine stress testing may serve as a marker for the future development of PE: an LVSV reserve of <1 was associated with a twofold increase in the risk of future PE relative to those with an LVSV reserve ≥1; 2) a decreased LVSV reserve was associated with PE independent of age, sex, LVEF, inducible LV wall motion abnormalities, and other risk factors for PE or congestive heart failure ($p = 0.002$); and 3) an increase in the stress/resting ratio of ventriculovascular stiffness (measured as brachial $PP/LVSV_i$ for body surface area or stress-induced aortic distensibility) was associated with future PE in the absence of dobutamine-induced LV wall motion abnormalities indicative of ischemia. This increase in cardiovascular stiffening during intravenous dobutamine stress testing may contribute to the mechanism by which LVSV could be limited during stress in the absence of inducible LV wall motion abnormalities indicative of ischemia.

PE can occur in individuals with either a decreased or preserved LVEF (4,16,17). To this end, we assessed individuals with an LVEF ranging from 33% to 77% and found that impaired LVSV reserve during dobutamine-induced stress was associated with future PE in those with an LVEF <50% or ≥50% ($p = 0.002$). To address whether inducible LV wall motion abnormalities observed during dobutamine-induced stress accounted for the decrease in LVSV reserve, we performed stratified analyses (Table 3) in individuals without dobutamine-induced LV wall motion abnormalities indicative of ischemia. In those participants without inducible LV wall motion abnormalities indicative of ischemia during dobutamine-induced stress, impaired augmentation of the LVSV reserve remained associated with PE compared with controls ($p = 0.02$) (Fig. 3). Importantly, the results of these stratified analyses indicate that impaired LVSV reserve serves as a marker for future PE in the

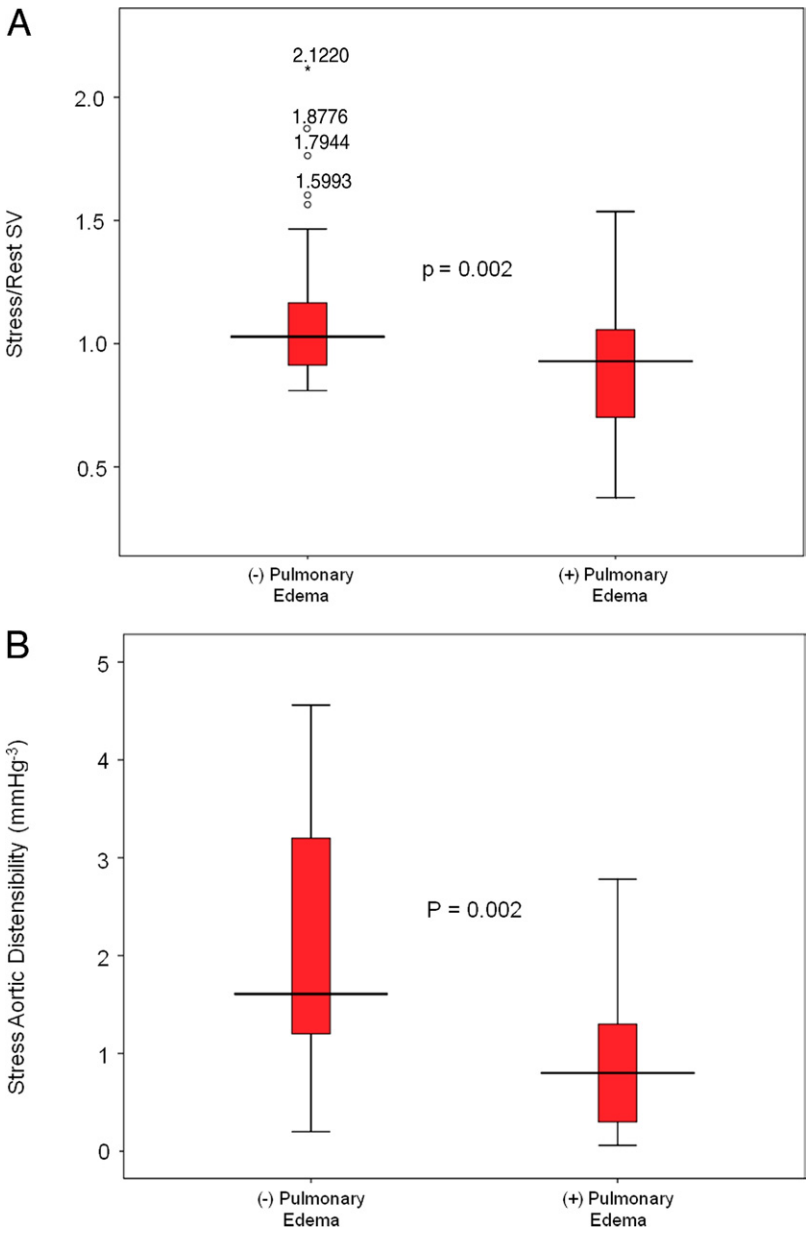

Figure 2 **Left Ventricular SV and Aortic Stiffness (All)**

Box-and-whisker plots of stress/rest left ventricular stroke volume (SV) (y-axis) **(A)** and peak stress aortic distensibility (y-axis) **(B)** measured during dobutamine cardiovascular magnetic resonance imaging. Pulmonary edema–negative and –positive groups are shown on the x-axis. Left ventricular stroke volume reserve was decreased and stress-induced aortic stiffness was increased in pulmonary edema–positive participants. In these plots, **lines within boxes** represent median values; the **top and bottom lines of the boxes** represent the 25th and 75th percentiles, respectively; and the **top and bottom whiskers outside the boxes** represent the smallest data value that is ≥1 to 1.5 quartile of the interquartile range and the largest data value that is ≤3 + 1.5 quartile of the interquartile range, respectively.

absence of conventional clinical markers of inducible ischemia used during dobutamine-induced stress.

Although our participants with PE exhibited a greater frequency of diabetes and hypertension, LVSV reserve was associated with PE independent of the presence of these conditions ($p < 0.001$). We recognize that clinical conditions such as renal failure, acute MI, chemotherapy-induced cardiomyopathy, valvular heart disease, and lung cancer may cause individuals to experience PE due to established causes. However, our analyses demonstrated that limits of LVSV reserve as well as increased ventriculovascular and aortic stiffness were predictive of future PE in the presence or absence of these conditions. In addition, a DCMR LVSV reserve of >1 was highly predictive of those who would remain PE free 2 years after stress testing.

Table 3 DCMR Findings in Participants With and Without Isolated Pulmonary Edema and No Inducible Ischemia

		Pulmonary Edema		p Value	p Value	
	All (n = 61)	Yes (n = 12)	No (n = 49)	p Value	Adjusted for Age, Sex	Adjusted for All Factors*
Resting EF	53 (45 to 56)	51 (41 to 54)	54 (47 to 56)	0.10	0.02	0.01
Resting EDV	109 (92 to 126)	113 (96 to 162)	107 (91 to 125)	0.26	0.09	0.10
Resting ESV	57 (43 to 72)	66 (37 to 113)	57 (43 to 69)	0.53	0.24	0.27
Resting SV	51 (44 to 58)	55 (46 to 61)	50 (44 to 55)	0.23	0.11	0.10
Stress EDV	99 (76 to 116)	110 (95 to 140)	99 (73 to 113)	0.10	0.16	0.07
Stress ESV	42 (30 to 61)	63 (44 to 101)	40 (28 to 58)	0.008	0.005	0.007
Stress SV	55 (47 to 59)	50 (35 to 58)	55 (49 to 59)	0.18	0.28	0.22
Resting EDVi	53 (45 to 69)	58 (47 to 90)	52 (45 to 66)	0.32	0.21	0.16
Resting ESVi	28 (22 to 38)	32 (20 to 63)	28 (22 to 35)	0.64	0.42	0.40
Resting SVi	25 (21 to 30)	30 (21 to 33)	25 (21 to 30)	0.42	0.45	0.30
Stress EDVi	50 (40 to 60)	59 (44 to 78)	50 (40 to 58)	0.15	0.15	0.12
Stress ESVi	23 (16 to 31)	29 (22 to 55)	20 (15 to 28)	0.02	0.02	0.02
Stress SVi	26 (23 to 31)	23 (18 to 31)	26 (25 to 31)	0.21	0.21	0.21
Resting PP/SV	1.2 (0.9 to 1.7)	1.1 (0.9 to 1.8)	1.2 (1.0 to 1.7)	0.67	0.34	0.28
Resting PP/SVi	2.6 (1.9 to 3.2)	2.4 (1.7 to 3.3)	2.6 (2.1 to 3.2)	0.68	0.41	0.31
Stress PP/SV	1.3 (1.0 to 1.6)	1.4 (1.2 to 2.1)	1.2 (0.9 to 1.6)	0.06	0.15	0.31
Stress PP/SVi	2.5 (2.0 to 3.3)	2.8 (2.4 to 4.0)	2.5 (1.9 to 3.2)	0.10	0.28	0.39
Stress/resting SV	1.3 (1.0 to 1.6)	0.9 (0.7 to 1.1)	1.0 (0.9 to 1.2)	0.04	0.06	0.07
Stress/resting SV	1.3 (−5.6 to 6.5)	−3.0 (−16.2 to 2.2)	1.5 (−5.0 to 7.9)	0.009	0.04	0.05
Stress/resting SVi	0.6 (−3.0 to 3.3)	−1.6 (−7.5 to 1.3)	0.8 (−2.8 to 4.0)	0.04	0.06	0.08
Stress-resting PP/SV	−0.0 (−0.2 to 0.3)	0.5 (0.1 to 0.8)	−0.1 (−0.6 to 0.5)	0.004	0.01	0.02
Stress/resting PP/SVi	−0.0 (−0.5 to 0.7)	0.8 (0.3 to 1.6)	−0.2 (−0.6 to 0.5)	0.003	0.008	0.01
Stress/resting PP/SV	1.0 (0.8 to 1.3)	1.4 (1.1 to 1.6)	0.9 (0.8 to 1.2)	0.002	0.004	0.008

Values are expressed as median (interquartile range). *Factors included in the multivariate model are age, sex (male), body mass index, previous myocardial infarction, hypertension, diabetes mellitus, hypercholesterolemia, and smoking.

DCMR = dobutamine cardiovascular magnetic resonance; EDV = end-diastolic volume; EDVi = end-diastolic volume index; EF = ejection fraction; ESV = end-systolic volume; ESVi = end-systolic volume index; PP/SV = pulse pressure/stroke volume; PP/SVi = pulse pressure/stroke volume index; SV = stroke volume; SVi = stroke volume index.

Why would decreased LVSV reserve serve as a marker for future PE? In patients with normal cardiovascular performance, cardiac output increases during stress due to an increase in heart rate, enhanced venous return to the right heart due to recruitment of blood from peripheral veins, and an increase in LVSV due to a decrease in LV end-systolic volume and maintenance or increase in LVEDV (18). We found that patients in whom acute PE subsequently developed had a decreased ability to increase LVSV in response to pharmacologic stress. In this study, we do not have information regarding right ventricular stroke volume; however, if LVSV failed to increase during exercise or volume challenge, an increase in right ventricular stroke volume could result in displacement of blood into the lungs, increase in left atrial pressure, and the development of PE (19–21).

It is important to note that we used dobutamine-induced stress rather than exercise to induce cardiovascular stress. We selected intravenous dobutamine because of its ease of clinical implementation, and one can collect images for measuring LV volumes simultaneously with the intravenous infusion. The stress produced by dobutamine-induced stress differs from exercise in 2 major respects (22). First, walking, running, or biking stimulates lower extremity muscle contraction and facilitates recruitment of venous blood into the central circulation. This, in turn, increases right ventricular end-diastolic volume and LVEDV (23). Intravenous dobutamine does not produce this effect, and, as shown in Table 2, we did not see maintenance or an increase in LVEDV in our subjects. In fact, LVEDV decreased in our participants, and thus the majority of our differences in LVSV reserve were due to differences in stress-induced change in LVEDV. We note, however, that our study was not powered to identify differences in the LVEDV with stress in those with and without PE, and although the SD change in LVEDV with stress was large in the study, it is interesting that the median change in LVEDV was 12 ml versus 7 ml in those without as opposed to those with PE ($p = 0.20$). Perhaps a study of more participants would identify an association of stress-induced change in LVEDV and future pulmonary disease.

Second, intravenous dobutamine relaxes arterial tone, which is often manifest by a decrease in SBP during initial infusions of the drug (24). Exercise, however, often increases SBP (25) and in patients with noncompliant vasculature can increase SBP further (19,21). Both our group and others have shown that proximal aortic distensibility is decreased in patients with heart failure with or without a decreased LVEF. In participants without inducible LV wall motion abnormalities, there was a strong trend ($p = 0.08$) toward an increase in PP (a surrogate for aortic stiffness) in patients with (12 mm Hg) versus those without (4 mm Hg) future PE. Although intravenous dobutamine may not

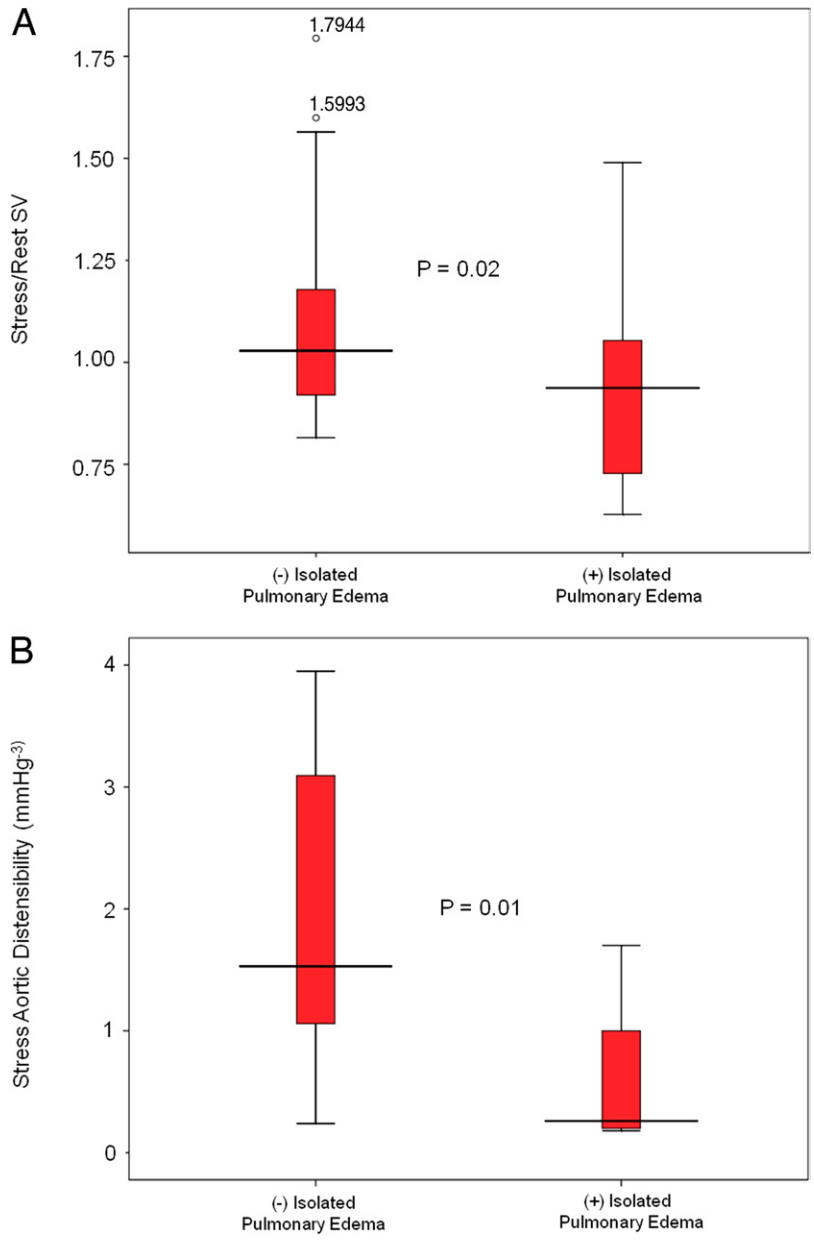

Figure 3 **Left Ventricular Stroke Volume and Aortic Stiffness (Isolated Pulmonary Edema)**

Box-and-whisker plots of stress/resting left ventricular stroke volume (y-axis) **(A)** and peak stress aortic distensibility (y-axis) **(B)** measured during dobutamine cardiovascular magnetic resonance imaging. Pulmonary edema–negative and –positive groups are shown on the x-axis. In participants with isolated pulmonary edema and no inducible left ventricular wall motion abnormalities indicative of ischemia during dobutamine stress testing, left ventricular stroke volume reserve was decreased and stress-induced aortic distensibility was increased relative to control subjects. In these plots, **lines within boxes** represent median values; the **top and bottom lines of the boxes** represent the 25th and 75th percentiles, respectively; and the **top and bottom whiskers outside the boxes** represent the smallest data value that is ≥1 to 1.5 quartile (interquartile range) and the largest data value that is ≤3 + 1.5 quartile (interquartile range), respectively.

increase pulmonary blood flow (LV pre-load) or SBP (LV afterload) to the same degree as exercise, our data demonstrate that the failure to increase LVSV during dobutamine infusion is associated with future pulmonary congestion.

Why was LVSV impaired during intravenous dobutamine infusion? Functionally apparent myocardial ischemia was not the cause of those with PE in our stratified analyses shown in Table 3 and Figure 3. It appears that increased arterial stiffness did contribute (Fig. 3B, Table 3). Several recent studies identified a relationship between increased aortic stiffness and LV function (5,13,26). Abnormal vascular stiffness increases LV afterload (27,28) and stimulates LV hypertrophy (29), both factors that may decrease LVSV during stress (5), respectively, by decreasing LV ejection

(19) and relaxation (30). Chattopadhyay et al. (16) recently reported an association of abnormal dobutamine-induced parameters of LV diastolic function and heart failure in the setting of a preserved LVEF. Similar to the associations that we observed with impaired LVSV reserve and future PE, our data show that patients in whom PE developed displayed increased stress/rest ratios of vascular stiffness and increased stress distensibility measures compared with patients in whom PE did not develop.

Study limitations. First, our design, similar to a case-control study, may not readily identify a variable in the study population that could influence our primary outcomes of LVSV reserve or cardiovascular stiffness. To this end, we matched our "control" population to include those of similar age, sex, and LVEF to our study (or case) population. In addition, we performed multivariable analyses that accounted for other clinical variables such as hypertension and diabetes that could influence the study results. Importantly, after accounting for these covariables, LVSV reserve and vascular stiffness remained associated with future PE.

Second, although our DCMR method of biplane LV volume analysis is similar to that used during dobutamine stress echocardiography, newer 3-dimensional techniques can measure LV volumes more accurately and in future studies decrease potential variance in volume-derived measures. Third, our measures of vascular stiffness and aortic distensibility incorporated brachial rather than central aortic PP assessments. It has been shown in some individuals that the brachial cuff pressure estimate of central aortic pressure may not accurately reflect central aortic pressure in those with stiff aortas or increasing heart rates (31,32). Although large patient studies, such as the MESA (Multiethnic Study of Atherosclerosis) (33) and the Dallas Heart Study (34) have used aortic distensibility as an outcome measure in >3,000 participants, other techniques, such as pulse wave velocity, are less dependent on brachial PP assessments. Fourth, our retrospective review of hospital records may have inadvertently omitted episodes of PE managed by physicians using oral (rather than intravenous) diuretics in an outpatient office setting. Other study designs could be implemented to capture these types of events and determine the association of PE with our measures of ventriculovascular stiffness. Finally, we wish to recognize that our stratified analyses were performed on relatively small samples, and there may be other variables, in addition to our measures of ventriculovascular stiffness, that could be significantly associated with further PE events.

Conclusions

Impaired LVSV reserve measured during dobutamine-induced cardiac stress may predict an episode of future PE. Increased arterial stiffness may impair LVSV augmentation during stress and therefore serve as a mechanism to induce PE in the absence of inducible LV wall motion abnormalities indicative of ischemia. As a result, stress-induced changes in LVSV and vascular stiffness measured during noninvasive stress testing may identify those at risk of future PE.

Reprint requests and correspondence: Dr. W. Gregory Hundley, Wake Forest University School of Medicine, 1 Medical Center Boulevard, Winston-Salem, North Carolina 27157-1045. E-mail: ghundley@wfubmc.edu.

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Key Words: dobutamine cardiovascular magnetic resonance ■ heart failure ■ stroke volume.