DOI: 10.1111/echo.12955
Echocardiography

ORIGINAL INVESTIGATION

The Prognostic Utility of Echo-Estimated Left Ventricular End-Diastolic Pressure–Volume Relationship in Stable Coronary Artery Disease: The Heart and Soul Study

Rakesh K. Mishra, M.D.,*† Jeremy Tietjens, M.D.,* Mathilda Regan, M.P.H.,† Mary A. Whooley, M.D.,*† and Nelson B. Schiller, M.D.*†

*University of California, San Francisco, San Francisco, California; and †San Francisco Veterans Affairs Medical Center, San Francisco, California

Background: While changes in the left ventricular end-diastolic pressure–volume relationship (LV-EDPVR) can be estimated using echocardiography, their prognostic utility in stable coronary artery disease (CAD) is unknown. Methods: Using echo-estimated LV end-diastolic volume index and diastolic function category, the relative position of the LV-EDPVR was defined in 901 participants with stable CAD as: (1) left-shifted, (2) right-shifted, or (3) intermediate. We then evaluated the association of LV-EDPVR position relative to the intermediate category with time to hospitalization for heart failure (HF) or cardiovascular (CV) death using Cox proportional hazards models. Results: During 7.0 ± 3.1 years of follow-up, there were 207 admissions for HF or CV deaths. Both leftward and rightward shifts of LV-EDPVR were associated with a significantly higher risk of HF or CV death (HR 1.73, 95% CI 1.15–2.62 and HR 6.75, 95% CI 4.02–11.31, respectively). In multivariable-adjusted models, these associations were attenuated but remained significant (HR 1.66, 95% CI 1.08–2.55 for left-shifted and HR 4.19, 95% CI 2.32–7.55 for right-shifted). The association of LV-EDPVR with HF or CV death was no longer significant after inclusion of *N*-terminal pro-brain natriuretic peptide level as a covariate. Conclusions: In stable CAD, echo-estimated leftward and rightward shifts in the LV-EDPVR are associated with HF and CV death. The loss of these associations after adjustment for *N*-terminal pro-brain natriuretic peptide level suggests that echo-estimated LV-EDPVR captures changes in LV filling pressure at any given LV end-diastolic volume. (Echocardiography 2015;00:1–8)

Key words: coronary artery disease, diastolic function, echocardiography, heart failure, left ventricular end-diastolic pressure

The relationship between left ventricular pressure and volume, a fundamental aspect of cardiac physiology, has traditionally been characterized using invasively determined pressure volume loops.[1–3] The left ventricular enddiastolic pressure–volume relationship (LV-EDPVR) is determined by the volume the LV chamber will assume for a given end-diastolic pressure, a reflection of LV distensibility.[4] Leftward or rightward shift of this relationship represents decreased or increased LV distensibility, respectively, and has been implicated in the underlying pathophysiology of congestive heart failure (CHF).[4,5]

Address for correspondence and reprint request: Rakesh K. Mishra, M.D., San Francisco Veterans Affairs Medical Center, 4150 Clement St. (111C), San Francisco, CA 94121. Fax: (415) 750-6950;
E-mail: rakesh.mishra@ucsf.edu

Evaluation of LV-EDPVR is not routinely performed in clinical practice due to the need for invasive hemodynamic measurements. In recent years, however, a growing literature describing noninvasive methods of determining LV-EDPVR has emerged. Klotz et al.[6] described a method of single-beat estimation of LV-EDPVR. More recently, Spevack et al.[7] applied this technique using echocardiography to patients with CHF and found the relative position of echo-estimated LV-EDPVR to be a significant predictor of mortality, independent of LV ejection fraction, and traditional Doppler indices of LV diastolic dysfunction.

The prognostic utility of noninvasively determined shifts in the LV-EDPVR has not, however, been studied in other populations, including in ambulatory patients with stable coronary artery disease (CAD). In this study, we investigated whether the relative position of the LV-EDPVR

would predict adverse cardiovascular outcomes in patients with stable CAD.

Methods:

Study Subjects:

The Heart and Soul study is a prospective cohort study of psychosocial factors and health outcomes in patients with stable coronary artery disease. Methods and objectives have been described previously.[8] Subjects were enrolled between September 2000 and December 2002 across two Veterans' Affairs Hospitals, one academic medical center, and nine public health clinics in the San Francisco Bay Area. Eligible patients had stable CAD defined by at least one of the following: history of MI, angiographic evidence of at least 50% stenosis in one or more coronary arteries, and evidence of exercise-induced ischemia by treadmill testing or history of coronary revascularization. Patients, who were unable to walk at least one block, were within 6 months of an acute coronary syndrome or planned to relocate out of the area within 3 years were excluded.

All subjects gave informed consent under protocols approved by the University of California, San Francisco, committee on human research, the research and development committee of the San Francisco Veterans Affairs Medical Center, the medical human subjects committee of Stanford University, the human subjects committee at the Veterans Affairs Palo Alto Health Care System, and the data governance board of the Community Health Network of San Francisco.

Comprehensive baseline data for each subject were acquired upon enrollment. Demographics, age, ethnicity, gender, smoking status, and medical history were determined by questionnaire. Study personnel measured patients' blood pressure, height and weight, obtained a resting electrocardiogram, and drew blood to estimate glomerular filtration rate (eGFR). Baseline medications were documented by review of patient prescription bottles. In addition, a complete transthoracic echocardiogram was performed.

Of the 1024 participants initially enrolled, 967 had complete echocardiographic assessment of the parameters relevant to our study. Subjects with moderate or greater mitral or aortic valvular stenosis or regurgitation ($n = 7$) or with indeterminate diastolic function category [$E/A \geq 1.5$ and systolic-dominant pulmonary venous flow; see below] ($n = 53$) were excluded. Because Doppler mitral inflow patterns cannot be used to reliably evaluate LV filling pressures in patients with atrial fibrillation,[9] these participants ($n = 6$) were excluded as well. The remaining 901 participants were included in our analysis.

Echocardiography:

Complete resting two-dimensional echocardiography and Doppler ultrasound examinations, including standard two-dimensional parasternal short-axis, apical two- and four-chamber, and subcostal views, were obtained at baseline using an Acuson Sequoia Ultrasound System (Siemens Medical Solutions USA, Inc., Mountain View, CA, USA). All echocardiograms were interpreted by a single, experienced cardiologist (N.B.S.) who was blinded to all other patient-specific variables.

LV end-diastolic and end-systolic volumes were estimated using the modified biplane method of discs.[10] LV ejection fraction was calculated as (LV end-diastolic volume − LV end-systolic volume)/LV end-systolic volume. LV mass was estimated using the truncated ellipsoid method and indexed to body surface area.[10] Mitral inflow velocities (E and A) were obtained in the apical four-chamber view using pulse-wave Doppler, as was pulmonary vein flow velocity. Pulmonary venous flow dominance pattern was determined using the maximum velocity-time integral. LV diastolic function was categorized using patterns of mitral inflow (E/A ratio) and pulmonary venous flow: Grade 1 (normal) was defined as $0.75 < E/A < 1.5$ with systolic predominant pulmonary venous flow; Grade 2 (impaired relaxation) as $E/A \leq 0.75$; Grade 3 (pseudo-normal) as $0.75 < E/A < 1.5$ with diastolic predominant pulmonary venous flow; Grade 4 (restrictive) as $E/A \geq 1.5$ with diastolic predominant pulmonary venous flow.[11] Participants with $E/A \geq 1.5$ and systolic-predominant pulmonary venous flow were considered to have indeterminate diastolic function category and were not included in this study. For the purpose of subsequent classification by relative EDPVR shift, we considered LV end-diastolic pressure (LV-EDP) elevated in subjects with either Grade 3 or 4 diastolic function.[6,11,12]

Predictors: Categorization of LV-EDPVR:

The LV-EDPVR was categorized into three groups using criteria previously described by Spevack[7] (Fig. 1). We used cutoffs recommended by the American Society of Echocardiography to define normal and severely increased left ventricular end-diastolic volume index (LV-EDVI).[10]Leftward shift of the LV-EDPVR was considered to be present in subjects with normal left ventricular size (LV-EDVI < 76 mL/m^2) despite increased LV-EDP (Grade 3 or 4 diastolic function category). Failure of the LV to dilate despite increased pressure reflects the decreased distensibility characteristic of a left-shifted LV-EDPVR. Subjects with severe dilation of the left ventricle (LV-EDVI > 97 mL/m^2) were classified as having rightward shift of LV-EDPVR regardless of LV-EDP. Because the EDVI

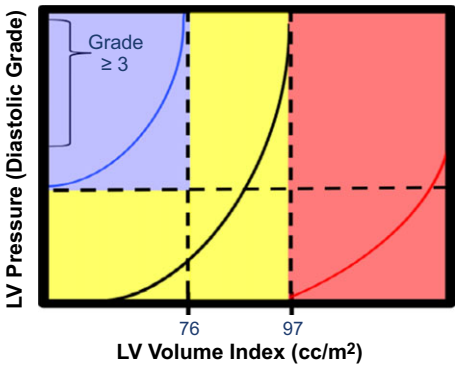


Figure 1. A schematic representation of the categorization of the noninvasively estimated left ventricular end-diastolic pressure volume relationship (LV-EDPVR). Right shift in the LV-EDPVR is defined by a LV end-diastolic volume index (LVEDVI) > 97 mL/m^2 (*red*). Left shift in the LV-EDPVR is defined as LVEDVI < 76 mL/m^2 and grade 3 or 4 diastolic function (*blue*). All other participants were considered to have intermediate LV-EDPVR (*yellow*).

has been shown to decrease up to a maximum of 20% in response to acute reduction of preload,[13,14] it seems likely that severely dilated ventricles would remain enlarged to some degree even after reduction in filling pressures to normal range, a pattern characteristic of a right-shifted LV-EDPVR. Subjects not meeting criteria for either leftward or rightward shift of LV-EDPVR were classified as intermediate.

Clinical Outcomes:

The primary outcome variable of interest in this study was the composite endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF). Specific criteria used in defining CV deaths and HF have been described previously.[15]

Statistical Analysis:

Baseline characteristics are reported as mean ± SD for continuous variables and as proportions for categorical variables. Differences between continuous variables were compared using two-tailed *t*-test and categorical variables using chi-square test. Unadjusted and multivariable-adjusted Cox proportional models were used to evaluate associations between LV-EDPVR category and time to HF hospitalization or CV death. Baseline variables with differences among LV-EDPVR categories ($P < 0.10$) were included as covariates in multivariate regression analyses. Event-free survival in each of the three EDPVR categories was compared using a Kaplan–Meier survival analysis. In addition, we evaluated the C-statistic, which is equivalent to the area under the receiver operating characteristics (ROC) curve, for LV-EDPVR as the single predictor of HF hospitalization or CV death.

Because leftward shift of the LV-EDPVR implies reduced distensibility, a mechanism believed to play a significant role in the pathogenesis of heart failure with preserved ejection fraction (HFpEF),[4,5,16] we performed a subgroup analysis on subjects with LVEF ≥ 50%. Data were analyzed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA).

Results:

Baseline Characteristics:

The study population was predominantly male with a high prevalence of hypertension and a moderate prevalence of diabetes and smoking (Table I).

Approximately 9% of the study participants met criteria for leftward shift in LV-EDPVR. These patients were more likely to have undergone CABG and had higher NT-proBNP levels compared with the intermediate category, but otherwise the groups were similar at baseline. Compared with those in the intermediate category, participants with a rightward shift in the LV-EDPVR (2%) had higher rates of prior myocardial infarction (MI), HF, β-blocker, ACE inhibitor (ACEi), and angiotensin receptor blocker (ARB) use and NT-proBNP levels, as well as lower systolic and diastolic blood pressure, eGFR, and body mass index (BMI). Patients with a rightward shift in the LV-EDPVR also had significantly higher LV mass indices, end-diastolic and end-systolic volume indices, and significantly lower ejection fractions than the intermediate group. On the other hand, the only significant echocardiographic difference between the leftward-shifted and intermediate groups was higher prevalence of Grade 3 or 4 diastolic dysfunction (100% vs. 2%) in the former group, which is a direct result of how the categories of LV-EDPVR were defined. Patients in the rightward shift group also had a higher prevalence (39%) of Grade 3 or 4 diastolic dysfunction than those in the intermediate category.

EDPVR Category and Outcomes:

During the mean follow-up of 7.0 ± 3.1 years, 207 patients (23%) experienced the primary outcome of either CV death or heart failure hospitalization. Participants with a rightward shift in the LV-EDPVR had the highest event rate (84%), compared with leftward-shifted (32%) and the intermediate (21%) category (Table I). Similarly, in the Kaplan–Meier analysis, participants with right-shifted LV-EDPVR had lower event-free survival compared with the intermediate group ($P < 0.001$), while there was a trend toward

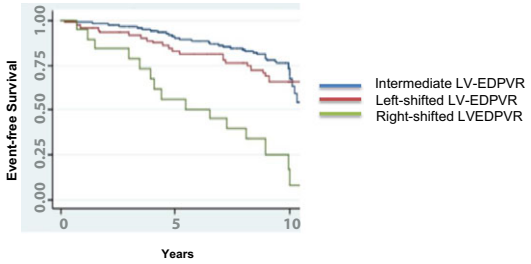
TABLE I

Baseline Characteristics of Participants by LV-EDPVR Category

	Cohort (n = 901)	Intermediate LV-EDVPR (n = 801)	Leftward LV-EDVPR (n = 81)	Rightward LV-EDVPR (n = 19)	P
Demographics					
Age (yrs)	66 ± 11	66 ± 1	66 ± 12	65 ± 10	0.82
Male (%)	735 (82)	649 (81)	68 (84)	18 (95)	0.26
Ethnicity					0.22
Black (%)	152 (17)	139 (17)	10 (12)	3 (16)	
Hispanic (%)	84 (9)	80 (10)	3 (4)	1 (5)	
White (%)	532 (59)	464 (58)	58 (72)	10 (53)	
Asian or Pacific Islander (%)	102 (11)	92 (12)	6 (7)	4 (21)	
Comorbidities					
Smoker (%)	186 (21)	164 (20)	16 (20)	6 (33)	0.41
Diabetes (%)	241 (27)	212 (26)	25 (31)	4 (22)	0.59
Hypertension (%)	635 (71)	570 (71)	55 (69)	10 (56)	0.32
History					
MI (%)	485 (54)	426 (54)	42 (52)	17 (94)	0.002
HF (%)	149 (17)	119 (15)	20 (25)	10 (56)	<0.001
PCI (%)	354 (40)	320 (40)	26 (32)	8 (44)	0.38
CABG (%)	314 (35)	256 (32)	52 (65)	6 (33)	<0.001
Biometrics					
Systolic BP (mmHg)	133 ± 21	133 ± 21	132 ± 22	119 ± 16	0.01
Diastolic BP (mmHg)	75 ± 11	75 ± 11	72 ± 10	64 ± 9	<0.001
BMI (kg/m^2)	28 ± 5	28 ± 5	29 ± 6	25 ± 3	0.006
Laboratory					
eGFR ($mL/min/1.73\ m^2$)	72 ± 22	73 ± 22	69 ± 22	64 ± 20	0.10
NT-proBNP (pg/mL)	152 (68, 366)	139 (63, 321)	301 (113, 619)	827 (340, 2972)	0.001
Echocardiography					
LV mass index (g/m^2)	98 ± 34	98 ± 34	96 ± 22	142 ± 31	<0.001
LV-EDVI (mL/m^2)	51 ± 18	50 ± 14	50 ± 12	120 ± 21	<0.001
LV-ESVI (mL/m^2)	21 ± 16	20 ± 13	20 ± 10	79 ± 23	<0.001
LVEF (%)	62 ± 10	63 ± 8	62 ± 10	35 ± 10	<0.001
LVEF ≥ 50% (%)	810 (90)	734 (92)	74 (91)	2 (10)	<0.001
Diastolic function grade > 2 (%)	99 (12)	11 (2)	81 (100)	7 (39)	<0.001
Medications					
Aspirin (%)	721 (80)	641 (80)	64 (79)	16 (84)	0.88
β-blocker (%)	523 (58)	454 (57)	53 (65)	16 (84)	0.02
ACEi/ARB (%)	447 (50)	389 (49)	43 (53)	15 (79)	0.03
Statin (%)	581 (64)	513 (64)	53 (65)	15 (79)	0.40
Diuretic (%)	252 (28)	217 (28)	26 (32)	9 (47)	0.11
Outcomes					
HF (%)	136 (15)	102 (13)	21 (26)	13 (68)	<0.001
CV Death (%)	119 (13)	100 (12)	12 (15)	7 (37)	0.008
HF or CV Death (%)	207 (23)	165 (21)	26 (32)	16 (84)	<0.001

LV-EDPVR = left ventricular end-diastolic pressure–volume relationship; MI = myocardial infarction; HF = heart failure; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft surgery; BP = blood pressure; BMI = body mass index; eGFR = estimated glomerular filtration rate; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; LV-EDVI = LV end-diastolic volume index; LV-ESVI = LV end-systolic volume index; LVEF = LV ejection fraction; ACEi/ARB = angiotensin-converting enzyme or angiotensin receptor blocker; CV = cardiovascular.

lower event-free survival for the left-shifted LV-EDPVR category (P = 0.097; Fig. 2). In unadjusted models, leftward shift in the LV-EDPVR was associated with an approximately twofold risk of HF hospitalization or CV death compared with the intermediate LV-EDPVR, while rightward shift was associated with a nearly sevenfold risk of these adverse events (Table II). After further adjustment for covariates, including history of HF, MI and coronary artery bypass surgery, systolic and diastolic blood pressure, and BMI, the risk associated with leftward and rightward shift in the LV-EDPVR was attenuated to 1.7-fold and approximately fourfold, respectively. With additional adjustment for LV end-systolic volume index, LV mass index, and medication use,



No. at Risk	Baseline	Year 5	Year 10
Intermediate LV-EDPVR	701	549	44
Left-shifted LV-EDPVR	75	55	6
Right-shifted LV-EDPVR	19	10	1

Figure 2. Kaplan-Meier plot for event-free survival by left ventricular end-diastolic pressure volume relationship (LV-EDPVR) category.

left-shifted LV-EDPVR was associated with an approximately twofold risk of HF hospitalization or CV death, while the association of right-shifted LV-EDPVR with these outcomes was no longer significant. In the fully adjusted model, with the inclusion of NT-proBNP level as a covariate, the association between left- or right-shifted LV-EDPVR and HF or CV death was no longer significant. LV-EDPVR performed modestly for the prediction of HF hospitalization or CV death (area under the curve: 0.56; 95% C.I. 0.52–0.60; P = 0.006).

EDPVR Category and Outcomes in Patients with Preserved Ejection Fraction:

In the subgroup of patients with preserved left ventricular systolic function (n = 808; Table SI), the proportion of patients with leftward shift in the LV-EDPVR (9%) was similar to the total cohort. However, only two participants with rightward shift had LVEF $\geq$ 50% and were, therefore, not included in this subgroup analysis. Compared with the intermediate group, the participants with leftward-shifted EDPVE were more likely to have a history of HF and surgical coronary revascularization and higher NT-proBNP level. Among participants with preserved LVEF, leftward shift in the LV-EDPVR carried an approximately twofold higher risk of HF or CV death compared with the intermediate group after adjustment for covariates (Table III). This risk was attenuated to 1.4-fold and was no longer significant after including NT-proBNP level as a covariate in the fully adjusted model.

Discussion:

The LV-EDPVR is an important measure of LV distensibility that has been evaluated noninvasively in recent studies using echocardiography.[6,7] In the present study, we demonstrated that both

TABLE II

Association of LV-EDPVR Category with Heart Failure or Cardiovascular Death

	Left-Shifted LV-EDPVR (n = 81)		Right-Shifted LV-EDPVR (n = 19)	
	HR (95% CI)*	P	HR (95% CI)*	P
Model 1	1.73 (1.15–2.62)	0.01	6.75 (4.02–11.31)	<0.001
Model 2	1.64 (1.07–2.52)	0.02	3.90 (2.23–6.83)	<0.001
Model 3	1.64 (1.07–2.51)	0.02	4.17 (2.32–7.49)	<0.001
Model 4	1.66 (1.08–2.55)	0.02	4.19 (2.32–7.55)	<0.001
Model 5	1.92 (1.20–3.06)	0.01	5.13 (0.60–43.68)	0.14
Model 6	1.60 (0.98–2.63)	0.06	3.23 (0.37–28.02)	0.29

HR = hazard ratio; LV-EDPVR = left ventricular end-diastolic pressure–volume relationship; MI = myocardial infarction; HF = heart failure; CABG = coronary artery bypass graft surgery; BP = blood pressure; BMI = body mass index; NT-proBNP = *N*-terminal pro-brain natriuretic peptide; LVESVI = LV end-systolic volume index; ACEi/ARB = angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.
*HR given with intermediate LV-EDPVR (n = 801) as referent.
Covariates for models: (1) Unadjusted; (2) History of HF, MI, CABG; (3) + Systolic and diastolic BP, BMI; (4) + β-blocker and ACEi/ARB use; (5) + LVESVI, LV mass index; (6) + NT-proBNP level.

TABLE III

Association of Left-Shifted LV-EDPVR with Heart Failure or Cardiovascular Death in Participants with Preserved LV Ejection Fraction

	Left-Shifted LV-EDPVR (n = 74)	
	HR (95% CI)*	P
Model 1	1.85 (1.19–2.88)	0.01
Model 2	1.82 (1.16–2.84)	0.01
Model 3	1.62 (1.02–2.57)	0.04
Model 4	1.64 (1.03–2.61)	0.04
Model 5	1.40 (0.86–2.28)	0.18

HR = hazard ratio; LV-EDPVR = left ventricular end-diastolic pressure–volume relationship; HF = heart failure; CABG = coronary artery bypass graft surgery; BP = blood pressure; NT-proBNP = *N*-terminal pro-brain natriuretic peptide.
*HR given with intermediate LV-EDPVR (n = 734) as referent.
Covariates for models: (1) Unadjusted; (2) Ethnicity; (3) + History of HF, CABG; (4) + Diastolic BP; (5) + NT-proBNP level.

leftward and rightward shifts in the noninvasively determined LV-EDPR were associated with HF and CV death in participants with stable CAD. Moreover, among participants with preserved LVEF, a leftward shift in the LV-EDPVR was independently associated with HF and CV death. These findings expand the literature by demonstrating the feasibility and prognostic utility of the noninvasively estimated LV-EDPVR in ambulatory patients with stable CAD, including those patients with preserved LV systolic function.

Assessment of LV diastolic function by Doppler echocardiography is routinely performed in clinical practice. Specific techniques employed in this context include assessment of mitral inflow pattern, mitral annular tissue velocity, and pulmonary venous flow.[11] Despite their widespread use, these techniques primarily measure indices of LV filling dynamics, which are related to but distinct from intrinsic passive diastolic properties of the myocardium.[17] Specifically, as these indices of LV filling dynamics change with LV filling volume, they cannot evaluate LV distensibility without a simultaneous assessment of LV volume.[18] Diastole, which consists of isovolumic relaxation and ventricular filling phases, contains both active and passive components.[19,20] Relaxation, characterized by the time constant of relaxation (tau), is an active process involving the removal of intracellular calcium and uncoupling of actin–myosin cross-bridges. Various insults such as hypoxia, ischemia, and abnormal calcium regulation may interfere with relaxation.[21] Conversely, LV compliance and its mathematical reciprocal, stiffness, are passive properties that are determined by intrinsic myocardial variables such as cytoskeletal architecture, extracellular matrix composition, wall thickness and chamber geometry, and that vary with filling pressure.[22–25] The distinct mechanisms underlying these processes imply that, in a given individual, "diastolic dysfunction" could potentially reflect abnormalities of active properties, passive properties, or both. Thus, combining Doppler-estimated filling pressures with echo-derived LV end-diastolic volume to determine the relative position of the LV-EDPVR may provide a more "global" evaluation of LV diastolic function.[18]

The natriuretic peptides, including *N*-terminal pro-brain natriuretic peptide (NT-proBNP), are released into the circulation in response to myocardial stretch and are validated serum biomarkers for elevated LV filling pressure.[26,27] We found a stepwise increase in NT-proBNP level from the intermediate LV-EDPVR group to the leftward-shifted group and then to the rightward-shifted group, consistent with stepwise increases in LV filling pressure. Furthermore, the loss of the association between LV-EDPVR category and HF or CV death after adjustment for NT-proBNP level suggests that our categorization of LV-EDPVR did indeed capture changes in LV filling pressure at any given LV end-diastolic volume.

Prior to the current study, the prognostic value of echo-determined LV-EDPVR position had only been assessed by Spevack et al.[7] in patients with CHF. Unlike the participants in our study, these participants were recruited from CHF clinics and the majority of them had reduced LV ejection fraction. However, similar to our findings, they reported a significant association of a left-shifted LV-EDPVR with mortality, while a rightward shift was associated with increased mortality only in elderly patients.[7] In their study, Spevack et al.[7] performed additional analyses using left atrial volume, instead of Doppler indices of LV diastolic function, as a surrogate for LV filling pressure and obtained similar associations between LV-EDPVR position and adverse events. We, on the other hand, demonstrated that our categorization of LV-EDPVR was indeed capturing elevated LV filling pressure by adjusting for NT-proBNP and observing attenuation of the association between LV-EDPVR position and adverse outcomes. Our study builds upon the findings reported by Spevack et al.[7] by extending the application of the noninvasively determined LV-EDPVR to an ambulatory population with stable CAD and a low prevalence of HF and to patients with preserved LV systolic function.

We have previously reported the prognostic utility of multiple echo-Doppler measures of LV diastolic dysfunction, including left atrial volume and mitral and pulmonary venous inflow patterns in this same cohort of patients with stable

CAD.[28–32] The association of these Doppler indices with adverse cardiovascular outcomes reflects the multiple mechanisms by which myocardial ischemia can impair diastolic function, including impairment of relaxation, myocardial hypertrophy and/or fibrosis, delayed untwisting, and diastolic dyssynchrony.[29,33–36] The combination of the Doppler indices of diastolic function with LV end-diastolic volume to approximate the relative position of LV-EDPVR may capture the effects of these various pathophysiologic effects of myocardial ischemia on LV diastolic function. In this study, the prognostic value of LV-EDPVR category, as evaluated by ROC analysis, was modest but significant.

Preclinical diastolic dysfunction describes the presence of echocardiographic evidence of diastolic dysfunction prior to the onset of symptomatic HF and is common in patients with stable CAD.[37–40] In addition, CAD is common among patients presenting with heart failure with preserved LV ejection fraction (HFpEF).[41] In our study, the left-shifted LV-EDPVR was defined as a normal LV end-diastolic volume index despite elevated LV filling pressure, suggesting reduced LV distensibility.[7] Among the subset of participants in our study with preserved LV systolic function, we found an independent association of a left-shifted LV-EDPVR with HF and CV death. This suggests that decreased LV compliance portends increased risk of adverse events among patients with stable CAD and preserved LV systolic function. Decreased LV compliance is thought to be one of the primary pathophysiologic processes in HFpEF.[4,5] Interestingly, in the subgroup of participants in our study with preserved LV ejection fraction, the majority (83%) had no history of HF despite having a left-shifted LV-EDPVR. Our results suggest that a left-shifted LV-EDPVR may be a useful marker of preclinical diastolic dysfunction and may herald progression to HFpEF.

Limitations:

As our study population consisted predominantly of middle-aged to elderly male veterans with stable CAD, our findings may not apply to other populations. Because we relied on a combination of mitral and pulmonary venous inflow velocities to evaluate diastolic function category, participants with $E/A \geq 1.5$ and systolic-dominant pulmonary venous flow could not be assigned to a diastolic function category unambiguously and were, therefore, excluded. Tissue Doppler measurement of mitral annular velocity may have aided in the assignment of these participants to an appropriate diastolic function category but was not performed in this study. Without comparison to an invasive catheter-based determination, it is possible that our noninvasive LV-EDPVR is not accurate. However, the attenuation of risk with adjustment for NT-proBNP suggests that our method does capture LV filling pressure accurately.

Conclusion:

In ambulatory participants with stable CAD, both leftward and rightward shifts in the noninvasively determined LV-EDPVR predicted HF hospitalization and CV death. Among participants with preserved LVEF, a leftward shift in the LV-EDPVR was an independent predictor of adverse CV events. The loss of these associations after adjustment for *N*-terminal pro-brain natriuretic peptide level suggests that echo-estimated LV-EDPVR captures changes in LV filling pressure at any given LV end-diastolic volume. These findings illustrate the feasibility and prognostic utility of the echo-determined LV-EDPVR.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. Baseline characteristics of participants with preserved LV ejection fraction by LV-EDPVR category.