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ORIGINAL RESEARCH

Left Ventricular Wall Stress and Incident Heart Failure in Elderly Community-Dwelling Individuals

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ABSTRACT

BACKGROUND Greater left ventricular (LV) wall stress is associated with adverse outcomes among patients with prevalent heart failure (HF). Less is known about the association between LV wall stress and incident HF.

OBJECTIVES The purpose of the study was to identify clinical factors associated with wall stress and test the association between wall stress and incident HF.

METHODS We studied 4,601 ARIC (Atherosclerosis Risk In Communities) study participants without prevalent HF who underwent echocardiography between 2011 and 2013. LV end systolic and diastolic wall stress (LVESWS, LVEDWS) were calculated from chamber and wall thickness, systemic blood pressure, and transmitral Doppler E/e' as a surrogate for LV end diastolic pressure. Incident HF was ascertained by International Classification of Diseases (ICD)-9/10 claims for hospitalized HF through December 31, 2016. We used Cox regression to test the association between wall stress and incident HF, adjusted for demographics, traditional cardiovascular risk factors, prevalent coronary artery disease and atrial fibrillation, creatinine, N-terminal
pro-B-type natriuretic peptide, troponin, triglycerides, C-reactive protein, LV ejection fraction, and LV mass.

RESULTS The cohort had a median age of 75 years and 58% women, with 18% identifying as Black. Median LVESWS and LVEDWS were 48.8 (25th-75th percentile: 39.3-60.1) and 18.9 (25th-75th percentile: 15.8-22.5) kdynes/cm^2, respectively. LVESWS and LVEDWS were modestly related (rho = 0.30, $P < 0.001$). Over 4.6 years of median follow-up (156 HF events), each 1 kdyne/cm^2 greater LVEDWS was significantly associated with higher risk of incident HF (HR: 1.03; 95% CI: 1.01-1.06), while LVESWS was not (HR: 1.00; 95% CI: 0.99-1.01).

CONCLUSIONS Among community-dwelling elderly individuals, greater LVEDWS is associated with a higher risk for incident HF. (JACC Adv. 2024;3:101262) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ARIC = Atherosclerosis Risk in Communities

HF = heart failure

LV = left ventricle

LVEDWS = left ventricular end diastolic wall stress

LVEF = left ventricular ejection fraction

LVESWS = left ventricular end systolic wall stress

PCWP = pulmonary capillary wedge pressure

TTE = transthoracic echocardiography

Wall stress is implicated in the pathogenesis of left ventricular (LV) remodeling and heart failure (HF) development and progression.[1,2] According to the law of Laplace, ventricular wall thickness increases in response to elevated pressures and/or chamber dimensions as an adaptive mechanism to decrease wall tension.[1] Persistent pressure overload activates signaling pathways that may induce cardiomyocyte fibrosis and pathologic hypertrophy,[3,4] thereby limiting this adaptation. In observational studies of patients with or without HF, echocardiographic wall stress is associated with LV hypertrophy and reduced systolic and diastolic function.[5-9] LV end systolic and end diastolic wall stress (LVESWS, LVEDWS) are characteristically elevated in patients with HF,[1,3,9] though whether they retain prognostic significance in its absence remains less clear. Although wall stress is not routinely quantified from transthoracic echocardiography (TTE), standard TTE acquisitions provide sufficient data to estimate LV wall stress, which has been validated against invasive angiography.[10] TTE-estimated wall stress may therefore provide a readily quantifiable, noninvasive parameter to understand HF development. The ARIC (Atherosclerosis Risk In Communities) study is a National Institutes of Health-sponsored prospective observational cohort in which TTE has been performed along with longitudinal follow-up for incident HF. We hypothesized that among ARIC participants without prevalent HF, greater wall stress is associated with a higher risk of incident HF. Using publicly available data from ARIC, we: 1) examined clinical factors associated with wall stress among individuals without prevalent HF; and 2) tested the association between TTE-estimated wall stress and incident HF events.

METHODS

STUDY COHORT. ARIC is a longitudinal observational study that enrolled 15,792 participants between 1987 and 1989 to investigate risk factors for cardiovascular disease in 4 U.S. communities (Forsyth County, North Carolina; Jackson, Mississippi; Washington County, Maryland; and Minneapolis, Minnesota). The study was approved by institutional review boards at each site, and participants provided written informed consent. A total of 6,538 individuals took part in the fifth ARIC visit between 2011 and 2013 with ascertainment of medical history and biospecimen collection, as previously described,[11,12] of which 5,597 participants also underwent TTE. Participants with a history of HF (n = 817), moderate or severe valvular disease (n = 85), and those in whom LVEDWS or LVESWS could not be calculated were excluded (n = 94), yielding an analytic cohort of 4,601 individuals.

ECHOCARDIOGRAPHY AND WALL STRESS. TTE was obtained on participants using a standardized protocol with subsequent transmission of images to the Cardiovascular Imaging Core Lab at Brigham and Women's Hospital, Boston, Massachusetts, USA, for offline analysis and quantification of cardiac structure and function, as previously described.[12] Wall stress was calculated using LV chamber dimensions and wall thicknesses obtained in the parasternal long-axis view, hemodynamic data obtained from Doppler imaging of the mitral valve and its annulus, as well as the aortic valve, and noninvasively measured systemic blood pressure (BP) using formulas previously validated against invasively obtained hemodynamic data.[10,13] LVESWS and LVEDWS were calculated as follows:

LVESWS = (0.334 × [SBP + peak aortic valve gradient] × LVIDs)/(PWT × [1 + PWT/LVIDs]), where SBP = systolic blood pressure, LVIDs = LV internal diameter at end systole, and PWT = posterior wall thickness. Systolic BP was measured from the brachial artery using a standard protocol. Aortic valve gradient was estimated from peak flow velocity using the simplified Bernoulli equation.

LVEDWS = (0.334 × PCWP × LVIDd)/(PWT × [1 + PWT/LVIDd]) where PCWP = pulmonary capillary wedge pressure and LVIDd = LV internal diameter at end diastole. The simplified formula of 4 + E/e' from early mitral inflow velocity (E) divided by the average of septal and lateral wall (e') was used to estimate PCWP.[14]

INCIDENT HEART FAILURE. The primary outcome was incident HF as determined by the ARIC events adjudication committee. Among ARIC cohort participants, potential HF events were captured through surveillance of hospitalizations with International Classification of Diseases-9th Revision or-10th Revision codes (code 428 or I50 in any position) and/or a HF key word listed at discharge, a death certificate including HF among the listed causes, or outpatient HF diagnosis reported during a follow-up phone call. Records from these events were then reviewed by the ARIC HF event adjudication committee using a previously validated approach.[11,15] In ARIC, HF with preserved ejection fraction is defined at a threshold LV ejection fraction (LVEF) of 50% or greater. The follow-up period was the time elapsed from the date of visit 5 to the date of HF hospitalization or death,

with censoring at the date of last contact for those lost to follow-up or December 31, 2016. Deaths were ascertained through annual phone calls to participants or their kin and ongoing surveillance of health department death certificate files.

DEMOGRAPHICS, ANTHROPOMETRICS, AND CLINICAL CHARACTERISTICS. Prevalent hypertension, diabetes, smoking status, coronary artery disease, and atrial fibrillation/flutter were defined as present as previously described.[16] Body mass index was calculated from weight and height. Hypertension was defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or use of antihypertensive medications at visit 5. In ARIC, an established standardized protocol was used to define the presence of coronary heart disease.[17,18] This included adjudicated myocardial infarction, silent myocardial infarction diagnosed by electrocardiogram changes, or coronary revascularization. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin-T were measured using an electrochemiluminescence immunoassay implemented on a Roche Cobas e411 analyzer (Roche Diagnostics). C-reactive protein was measured in specimen using a high sensitivity immunonephelometric assay implemented on a BNII nephelometer (Siemens Healthcare Diagnostics). Glucose and triglycerides were measured using standard clinical assays.

STATISTICAL ANALYSIS. Participants were categorized according to quartiles of LVESWS and LVEDWS, with summary statistics for clinical characteristics and cardiac structure and function calculated as counts (percentages) and median (25th-75th percentile) and compared using Fisher's exact, Pearson's chi-squared, or Wilcoxon rank-sum tests, as appropriate. Cross-sectional correlates of wall stress were examined in multivariable linear regression with parameters selected a priori with potential multicollinearity assessed by variance inflation factor. A history of hypertension, which includes use of antihypertensive medications, as well as systolic and diastolic BP measured at visit 5, were included in multivariable-adjusted models. We performed complete case analysis, such that individuals with missing data for covariates were not included in regression analyses. Missingness was less than 5% for each covariate. Spearman rank correlation was used to examine the association between LVEDWS and LVESWS. The risk of incident HF across the spectrum of LVEDWS and LVESWS was assessed using multivariable Cox regression adjusted for demographics, anthropometrics, and clinical characteristics. The final model included simultaneous adjustment for both LVEDWS and LVESWS to assess their independent associations with incident HF risk. Wall stress measures were modeled using linear terms on the risk of incident HF as examination for a nonlinear relationship using restricted cubic splines was not significant. The proportional hazards assumption was tested and not violated. In order to account for death before HF onset, Cox models were repeated for the composite outcome of incident HF or death. Sensitivity analyses were performed following recalculation of PCWP as: (1.29 · E/e' lateral) + 1.9 or E/e' alone.[19] All analyses were conducted using Stata v14.0 or higher (Stata Corp) with 2-sided P values <0.05 considered significant.

RESULTS

The analytic cohort of 4,601 individuals was elderly (median age 75 years), predominantly female (58%), with 18% of participants identifying as Black. Hypertension, diabetes, and coronary artery disease were prevalent in 72%, 30%, and 10% of individuals, respectively. Characteristics of ARIC participants according to quartile of LVEDWS and LVESWS are shown in **Table 1**. Both LVEDWS and LVESWS followed a right-skewed distribution. The median LVEDWS and LVESWS were 18.9 (25th-75th percentile: 15.8-22.5) and 48.8 (25th-75th percentile: 39.3-60.1) kdynes/cm^2 in the 4,601 individuals without prevalent HF, which were significantly lower than in the 817 participants with prevalent HF at visit 5 (LVEDWS: 20.1 [25th-75th percentile: 16.1-25.4] and LVESWS 51.8 [25th-75th percentile: 41.2-66.5] kdynes/cm^2, $P < 0.001$ for both).

CORRELATES OF WALL STRESS. **Figure 1** illustrates the correlation between LVEDWS and LVESWS (Spearman's rho = 0.30, $P < 0.001$). Results from multivariable adjusted regression to identify correlates of wall stress are displayed in **Table 2**. Variation in the correlates of LVEDWS and LVESWS was evident. For example, higher systolic BP and NT-proBNP were significantly associated with higher LVEDWS and LVESWS, while Black race, higher heart rate, triglycerides, and LVEF were associated with lower values for both wall stress measures. Age and female sex were inversely associated with LVESWS while positively related to LVEDWS. A few characteristics are specifically associated with LVEDWS but not LVESWS, namely, body mass index, creatinine, and C-reactive protein. Current smoking is associated with LVEDWS with borderline significance ($P = 0.049$). In contrast, characteristics significantly

TABLE 1 Baseline Clinical Characteristics According to Quartiles of Wall Stress

	LVESWS, kdynes/cm²				LVEDWS, kdynes/cm²			
	Quartile 1 <39.31 (n = 1,151)	Quartile 2 39.31 to <48.83 (n = 1,150)	Quartile 3 48.83 to <60.11 (n = 1,150)	Quartile 4 ≥60.11 (n = 1,150)	Quartile 1 <15.82 (n = 1,151)	Quartile 2 15.82 to <18.88 (n = 1,150)	Quartile 3 18.88 to <22.50 (n = 1,150)	Quartile 4 ≥22.50 (n = 1,150)
Age, y	75 (71-79)	74 (71-79)	75 (71-79)	75 (71-79)	74 (71-79)	74 (71-79)	74 (71-79)	75 (72-80)
Female	61	58	59	55	49	57	62	66
Black	18	18	16	18	23	18	16	14
Hypertension	71	70	69	77	68	72	70	77
Diabetes	34	31	29	27	30	30	30	30
CAD	8	10	11	11	10	10	7	12
Atrial fibrillation	5	5	4	5	5	4	4	5
Medication use								
Beta-blocker	26	27	29	31	24	26	29	33
ACE inhibitor	24	21	22	19	21	23	20	22
ARB	10	9	10	10	9	10	10	10
MRA	2	1	1	1	1	2	2	2
Loop diuretic	6	6	4	6	6	4	6	8
BMI, kg/m²	28.1 (25.1-31.5)	28.0 (24.9-31.3)	27.5 (24.5-31.1)	27.3 (24.7-30.8)	27.8 (24.8-31.2)	27.7 (24.8-31.0)	27.8 (25.0-31.0)	27.7 (24.6-31.7)
Heart rate, beats/min	66 (58-73)	64 (58-72)	64 (58-71)	63 (57-71)	67 (60-75)	65 (58-72)	64 (57-70)	63 (57-70)
Systolic BP, mm Hg	123 (113-134)	127 (117-138)	130 (120-140)	137 (126-149)	127 (117-139)	128 (118-139)	129 (119-141)	132 (119-144)
Diastolic BP, mm Hg	63 (57-70)	65 (59-73)	67 (61-74)	69 (62-76)	67 (60-75)	67 (60-73)	66 (60-73)	66 (59-73)
NT-proBNP, pg/mL	107 (56-213)	113 (58-221)	120 (65-225)	149 (79-285)	102 (53-210)	112 (61-209)	126 (65-228)	156 (80-302)
hs-cTnT, pg/mL	0.011 (0.007-0.016)	0.010 (0.007-0.015)	0.010 (0.007-0.014)	0.011 (0.007-0.016)	0.010 (0.007-0.015)	0.010 (0.007-0.015)	0.010 (0.007-0.015)	0.011 (0.007-0.016)
Creatinine, mg/dL	0.90 (0.78-1.08)	0.91 (0.78-1.07)	0.90 (0.77-1.06)	0.92 (0.78-1.08)	0.94 (0.80-1.10)	0.91 (0.78-1.09)	0.89 (0.76-1.05)	0.89 (0.76-1.06)
eGFR, ml/min/1.73 m²	61 (49-74)	63 (49-76)	63 (51-76)	63 (50-78)	63 (50-76)	64 (51-77)	63 (50-75)	61 (49-76)
Glucose, mg/dL	106 (98-120)	106 (98-120)	106 (97-117)	104 (97-117)	106 (98-118)	106 (98-118)	106 (97-119)	106 (97-120)
TAG, mg/dL	115 (88-152)	114 (86-154)	109 (83-146)	107 (83-147)	111 (84-149)	113 (86-150)	113 (85-156)	109 (85-147)
CRP, mg/dL	1.97 (0.97-4.16)	1.87 (0.92-4.11)	1.89 (0.87-3.82)	1.96 (0.97-4.08)	1.87 (0.86-4.10)	1.88 (0.92-3.82)	1.96 (0.98-4.29)	1.99 (0.97-4.12)

Values are median (25th-75th percentile) or %.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; hs-cTnT = high-sensitivity cardiac troponin T; LVEDWS = left ventricular end diastolic wall stress; LVESWS = left ventricular end systolic wall stress; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TAG = triglycerides.

associated with LVESWS, but not LVEDWS, included coronary artery disease, atrial fibrillation or flutter, troponin, glucose, and LV mass index.

WALL STRESS AND CARDIAC STRUCTURE AND FUNCTION. Cardiac structure and function according to quartiles of LVESWS and LVEDWS are shown in Tables 3 and 4. Participants with higher LVESWS and LVEDWS were more likely to have eccentric LV hypertrophy, while those with lower LVESWS and LVEDWS were more likely to have concentric LV hypertrophy. LVESWS is inversely associated with LVEF and LV mass index, while LVEDWS is positively associated with LVEF and LV mass index. E/A increased with higher LVEDWS but did not differ significantly across quartiles of LVESWS. Both LVESWS and LVEDWS are positively associated with left atrial volume index, but only LVEDWS is associated with higher tricuspid regurgitant velocity as a marker of pulmonary artery pressure. LVESWS was inversely associated with absolute systolic longitudinal and circumferential systolic strain, while LVEDWS did not associate with longitudinal strain and was positively associated with circumferential strain.

Figure 2 demonstrates the relation of wall stress with patterns of LV geometry. Both LVESWS and LVEDWS were lower among those with concentric hypertrophy compared with normal morphology, albeit with overlap (median LVESWS 41.6 vs 55.3 kdynes/cm², $P < 0.001$; median LVEDWS 17.0 vs 20.1 kdynes/cm², $P < 0.001$). LVEDWS was higher for individuals with eccentric hypertrophy vs normal geometry (median 21.5 vs 20.1 kdynes/cm², $P < 0.001$), while LVESWS was similar between individuals with eccentric hypertrophy and normal geometry (median 54.2 vs 55.3 kdynes/cm², $P = 0.506$).

WALL STRESS AND INCIDENT HF. Over a median follow-up of 4.6 years, 156 individuals developed incident HF. In multivariable Cox regression mutually adjusted for LVEDWS and LVESWS, each 1-unit increase in LVEDWS was significantly associated with an increased risk of incident HF (HR: 1.03; 95% CI: 1.01-1.06; $P = 0.003$) (Central Illustration), while LVESWS was not (HR: 1.00; 95% CI: 0.99-1.01;

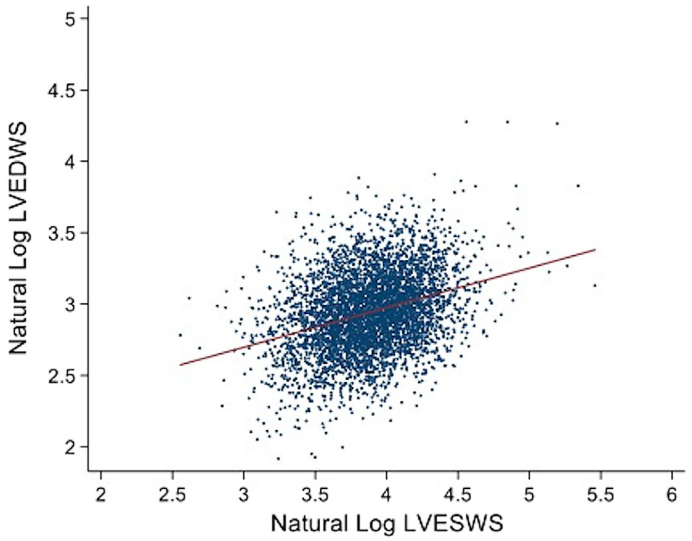
P = 0.888). The associations between wall stress measures and HF were linear. These results were independent of other risk markers for HF, including age, NT-proBNP, troponin, LVEF, and LV mass index. When accounting for wall stress, LVEF was not an independent predictor of incident HF (HR: 0.99; 95% CI: 0.97-1.02; P = 0.610). Results were similar when LVEDWS and LVESWS were modeled individually. The association between LVEDWS and incident HF was consistent regardless of method for estimating PCWP (Nagueh PCWP, HR: 1.03 [95% CI: 1.01-1.05] or E/e', HR: 1.04 [95% CI: 1.01-1.06]).

Of the 156 individuals who developed incident HF, 133 (85%) had LVEF data available in the medical record in relation to the HF event. Of these 133 HF events in which data regarding LVEF could be ascertained, approximately 53% were classified as having preserved ejection fraction. The 23 participants in whom LVEF data were not available in relation to the HF event were not included in the calculation of proportion of incident HF with preserved compared with reduced LVEF. Visit 5 LVEDWS values were similar between those with incident HF with preserved and reduced LVEF, median 20.7 (25th-75th percentile: 17.3-27.7) and 20.9 (16.0-26.1) kdynes/cm^2, respectively.

A total of 509 individuals developed incident HF or died over a median of 5 years of follow-up. In multivariable Cox regression simultaneously adjusted for LVEDWS and LVESWS, as well as other covariates, each 1-unit increase in LVEDWS was significantly associated with an increased risk of incident HF or death (HR: 1.02; 95% CI: 1.01-1.04; P = 0.006), while LVESWS did not (HR: 1.00; 95% CI: 0.99-1.01; P = 0.808). LVEDWS was not, however, significantly associated with all-cause mortality in the 407 individuals who died over the follow-up period (HR: 1.01; 95% CI: 0.99-1.03; P = 0.395).

Addition of LV internal diameter in diastole, posterior wall thickness, or left atrial volume index to the model did not attenuate the association between LVEDWS and incident HF. In contrast, when both E/e' and LVEDWS were included in the model, neither were significantly associated with the risk of incident HF (E/e', HR: 1.02, 95% CI: 0.98-1.06, P = 0.447; LVEDWS, HR: 1.02, 95% CI: 0.99-1.06, P = 0.211). Substituting E/e' for LVEDWS also demonstrated a significant association with the risk of incident HF (HR: 1.04, 95% CI: 1.01-1.06, P = 0.005), independent of LV internal diameter, posterior wall thickness, or left atrial volume index.

FIGURE 1 Correlation Plot of LVESWS and LVEDWS at ARIC Visit 5



Spearman rank correlation was used to examine the association between LVEDWS and LVESWS. Wall stress is presented in kdynes/cm^2. LVEDWS = left ventricular end diastolic wall stress; LVESWS = left ventricular end systolic wall stress.

DISCUSSION

Although substantial advances for treatment of HF have reduced morbidity and mortality, the incidence of HF remains high and is expected to increase with aging of the U.S. population, supporting the need for primary prevention.[20] In a community-dwelling cohort of elderly individuals without prevalent HF, we examined correlates and the prognostic significance of noninvasively estimated wall stress using echocardiography. Our principal findings are: 1) LVEDWS and LVESWS are modestly correlated; 2) clinical correlates of LVEDWS and LVESWS vary; and 3) greater LVEDWS, but not LVESWS, is associated with higher risk for incident HF. Collectively, these data may enhance understanding of cardiac structure and function in HF development and inform primary prevention strategies for HF.

Wall stress theory is frequently cited to explain the transition from physiologic LV hypertrophy to pathologic ventricular remodeling and subsequent HF; yet, few human studies have investigated wall stress with incident cardiovascular endpoints.[1] Therefore, in a community dwelling cohort of elderly individuals, we examined correlates of LVEDWS and LVESWS and the associations with the risk of incident HF. To our knowledge, we are the first to report noninvasively measured wall stress as a predictor of incident HF risk. In the LIFE (Losartan Intervention for End Point Reduction in Hypertension) study, myocardial oxygen demand was estimated from the triple product of LVESWS, LV mass, and heart rate

TABLE 2 Multivariable Adjusted Correlates of Left Ventricular Wall Stress

	LVESWS			LVEDWS		
	Beta Coefficient	95% CI	*P* Value	Beta Coefficient	95% CI	*P* Value
Age, per 1 y	**−0.154**	**−0.259 to −0.049**	**0.004**	**0.038**	**0.001-0.075**	**0.043**
Female	**−2.138**	**−3.305 to −0.972**	**<0.001**	**1.573**	**1.161-1.985**	**<0.001**
Black	**−2.287**	**−3.667 to −0.907**	**0.001**	**−1.220**	**−1.708 to −0.732**	**<0.001**
BMI, per 1 kg/m^2	−0.016	−0.115 to 0.083	0.75	**0.047**	**0.012-0.081**	**0.009**
Current cigarette use	0.140	−0.540 to 0.821	0.69	**−0.241**	**−0.482 to −0.001**	**0.049**
Hypertension	−0.870	−2.032 to 0.293	0.14	0.256	−0.155 to 0.667	0.22
CAD	**2.407**	**0.746-4.067**	**0.005**	0.430	−0.1575 to 1.017	0.15
Atrial fibrillation/flutter	**−2.732**	**−5.045 to −0.420**	**0.021**	−0.292	−1.110 to 0.526	0.48
Diabetes	0.638	−0.645 to 1.922	0.33	0.433	−0.021 to 0.887	0.062
Heart rate, per 1 beat/min	**−0.094**	**−0.141 to −0.047**	**<0.001**	**−0.072**	**−0.089 to −0.056**	**<0.001**
SBP, per 1 mm Hg	**0.353**	**0.324-0.382**	**<0.001**	**0.013**	**0.003-0.023**	**0.012**
Creatinine, per 1 mg/dL	−1.551	−3.123 to 0.021	0.053	**−0.729**	**−1.285 to −0.173**	**0.010**
Natural log NT-proBNP	**1.689**	**1.114-2.265**	**<0.001**	**0.585**	**0.381-0.788**	**<0.001**
Natural log hs-cTnT	**−1.028**	**−2.052 to −0.003**	**0.049**	0.118	−0.244 to 0.480	0.52
Glucose, per 1 mg/dL	**−0.029**	**−0.051 to −0.006**	**0.013**	0.004	−0.004 to 0.012	0.34
Triglycerides, per 1 mg/dL	**−0.010**	**−0.018 to −0.003**	**0.010**	**−0.003**	**−0.006 to −0.001**	**0.023**
CRP, per 1 mg/dL	0.054	−0.022 to 0.129	0.16	**0.036**	**0.009-0.063**	**0.008**
Ejection fraction, per 1%	**−0.950**	**−1.036 to −0.863**	**<0.001**	**−0.042**	**−0.073 to −0.012**	**0.006**
LV mass index, per 1 g/m^2	**−0.084**	**−0.112 to −0.055**	**<0.001**	−0.008	−0.018 to 0.002	0.12

Regression model adjusted for all variables shown. Beta coefficient corresponds to a 1-unit increase for continuous variables and the presence of the exposure for binary variables. **Bold** indicates $P < 0.05$.

BMI = body mass index; CAD = coronary artery disease; CRP = C-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; LV = left ventricular; LVEDWS = left ventricular end diastolic wall stress; LVESWS = left ventricular end systolic wall stress; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure.

TABLE 3 Echocardiographic Characteristics at ARIC Visit 5 According to Quartiles of LVESWS

		LVESWS, kdynes/cm^2				
	Missing, N	Quartile 1 <39.31 (n = 1,151)	Quartile 2 39.31 to <48.83 (n = 1,150)	Quartile 3 48.83 to <60.11 (n = 1,150)	Quartile 4 ≥60.11 (n = 1,150)	*P* Value
LVIDd, cm	0	**4.16 (3.91-4.49)**	**4.30 (4.01-4.63)**	**4.38 (4.07-4.71)**	**4.58 (4.24-4.93)**	**<0.001**
PWTd, cm	0	**0.97 (0.91-1.05)**	**0.93 (0.85-1.01)**	**0.87 (0.83-0.96)**	**0.86 (0.82-0.89)**	**<0.001**
IVSd, cm	2	**1.07 (0.97-1.19)**	**1.02 (0.93-1.14)**	**0.99 (0.90-1.11)**	**0.96 (0.88-1.07)**	**<0.001**
LVEDV, mL	118	**73 (60-91)**	**77 (64-94)**	**77 (64-95)**	**83 (67-101)**	**<0.001**
LVESV, mL	119	**23 (19-31)**	**26 (20-32)**	**27 (21-34)**	**29 (23-37)**	**<0.001**
LVEF, %	119	**67 (64-71)**	**66 (63-70)**	**66 (62-69)**	**64 (61-68)**	**<0.001**
LV mass index, g/m^2	9	**77 (67-88)**	**75 (64-87)**	**74 (64-87)**	**75 (66-86)**	**0.032**
RWT	0	**0.46 (0.43-0.51)**	**0.42 (0.39-0.47)**	**0.40 (0.37-0.44)**	**0.38 (0.35-0.41)**	**<0.001**
LV geometry	9					**<0.001**
Normal		9%	21%	26%	35%	
Concentric remod		26%	19%	14%	6%	
Concentric LVH		49%	31%	22%	11%	
Eccentric LVH		16%	29%	39%	48%	
LAVI, mL/m^2	41	**24.1 (19.7-29.1)**	**24.2 (19.9-29.4)**	**23.9 (19.7-29.0)**	**24.9 (20.9-30.4)**	**0.007**
E, cm/s	0	**65 (55-78)**	**64 (54-77)**	**65 (54-77)**	**62 (52-76)**	**0.003**
A, cm/s	140	**81 (69-92)**	**78 (67-90)**	**78 (67-89)**	**77 (66-90)**	**<0.001**
E/A	140	0.8 (0.7-0.9)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.70
e' lateral	15	6.7 (5.5-8.1)	6.9 (5.8-8.3)	6.9 (5.7-8.2)	6.9 (5.6-8.4)	0.082
e' septal	4	5.6 (4.7-6.5)	5.6 (4.8-6.7)	5.6 (4.8-6.6)	5.5 (4.7-6.5)	0.82
e' average	19	6.2 (5.3-7.3)	6.3 (5.4-7.4)	6.3 (5.5-7.3)	6.3 (5.4-7.4)	0.27
E/e'	0	**10.5 (8.6-13.0)**	**10.1 (8.5-12.4)**	**10.3 (8.4-12.4)**	**10.1 (8.3-12.3)**	**<0.001**
TR peak vel, cm/s	1,914	236 (218-256)	235 (217-252)	233 (216-252)	237 (221-256)	0.77
Peak long strain, %	267	**18.4 (16.8-19.9)**	**18.6 (16.9-19.8)**	**18.4 (16.6-19.9)**	**18.0 (16.3-19.5)**	**<0.001**
Peak circ strain, %	1,154	**29.1 (26.5-31.1)**	**28.7 (26.3-30.7)**	**28.5 (25.9-30.6)**	**27.4 (24.7-29.6)**	**<0.001**

Values are median (25th-75th percentile) or %.

TABLE 4 Echocardiographic Characteristics at ARIC Visit 5 According to Quartiles of LVEDWS

		LVEDWS, kdynes/cm²				
	Missing, N	Quartile 1 <15.82 (n = 1,151)	Quartile 2 15.82 to <18.88 (n = 1,150)	Quartile 3 18.88 to <22.50 (n = 1,150)	Quartile 4 >=22.50 (n = 1,150)	*P* Value
LVIDd, cm	0	**4.16 (3.92-4.48)**	**4.30 (4.01-4.63)**	**4.43 (4.10-4.75)**	**4.54 (4.20-4.89)**	**<0.001**
PWTd, cm	0	**0.99 (0.88-1.09)**	**0.91 (0.85-0.99)**	**0.88 (0.84-0.95)**	**0.86 (0.79-0.93)**	**<0.001**
IVSd, cm	2	**1.07 (0.96-1.19)**	**1.01 (0.92-1.11)**	**0.99 (0.91-1.10)**	**0.99 (0.90-1.10)**	**<0.001**
LVEDV, mL	118	79 (64-96)	77 (64-95)	77 (63-94)	76 (63-95)	0.13
LVESV, mL	119	**27 (20-35)**	**26 (20-33)**	**26 (20-33)**	**25 (20-34)**	**0.016**
LVEF, %	119	**65 (61-69)**	**66 (63-69)**	**66 (63-70)**	**66 (62-70)**	**0.008**
LV mass index, g/m²	9	**75 (65-89)**	**73 (64-86)**	**75 (66-85)**	**77 (67-88)**	**0.041**
RWT	0	**0.47 (0.43-0.52)**	**0.42 (0.39-0.46)**	**0.40 (0.37-0.43)**	**0.38 (0.34-0.41)**	**<0.001**
LV geometry	9					**<0.001**
Normal		11%	24%	28%	28%	
Concentric remod		37%	17%	8%	3%	
Concentric LVH		43%	32%	23%	15%	
Eccentric LVH		9%	27%	41%	54%	
LAVI, mL/m²	41	**23.3 (19.2-28.9)**	**24.8 (19.8-28.7)**	**24.2 (20.1-29.4)**	**25.5 (21.1-31.2)**	**<0.001**
E, cm/s	0	**55 (46-64)**	**61 (53-71)**	**67 (58-78)**	**78 (65-91)**	**<0.001**
A, cm/s	140	**73 (62-84)**	**76 (65-86)**	**80 (68-91)**	**87 (76-101)**	**<0.001**
E/A	140	**0.7 (0.6-0.9)**	**0.8 (0.7-0.9)**	**0.8 (0.7-1.0)**	**0.9 (0.7-1.1)**	**<0.001**
e' lateral	15	**7.6 (6.3-9.3)**	**7.3 (6.0-8.6)**	**6.7 (5.6-7.9)**	**6.0 (4.9-7.1)**	**<0.001**
e' septal	4	**5.9 (5.0-7.2)**	**5.8 (5.0-6.8)**	**5.5 (4.8-6.4)**	**5.1 (4.4-5.9)**	**<0.001**
e' average	19	**6.9 (5.8-8.1)**	**6.6 (5.7-7.6)**	**6.2 (5.4-7.1)**	**5.6 (4.8-6.5)**	**<0.001**
E/e'	0	**8.0 (6.8-9.2)**	**9.4 (8.2-10.8)**	**10.8 (9.5-12.3)**	**13.6 (11.8-16.1)**	**<0.001**
TR peak vel, cm/s	1914	**231 (214-249)**	**234 (217-252)**	**234 (217-252)**	**241 (224-261)**	**<0.001**
Peak long strain, %	267	18.3 (16.6-19.7)	18.5-(16.8-19.9)	18.5 (16.8-19.8)	18.1 (16.4-19.8)	0.28
Peak circ strain, %	1,154	**27.9 (25.4-30.6)**	**28.4 (26.1-30.4)**	**28.8 (26.3-30.8)**	**28.5 (25.8-30.9)**	**<0.001**

Values are median (25th-75th percentile) or %. Bold indicates $P < 0.05$. Peak longitudinal systolic strain presented as an absolute rather than raw (negative) value.

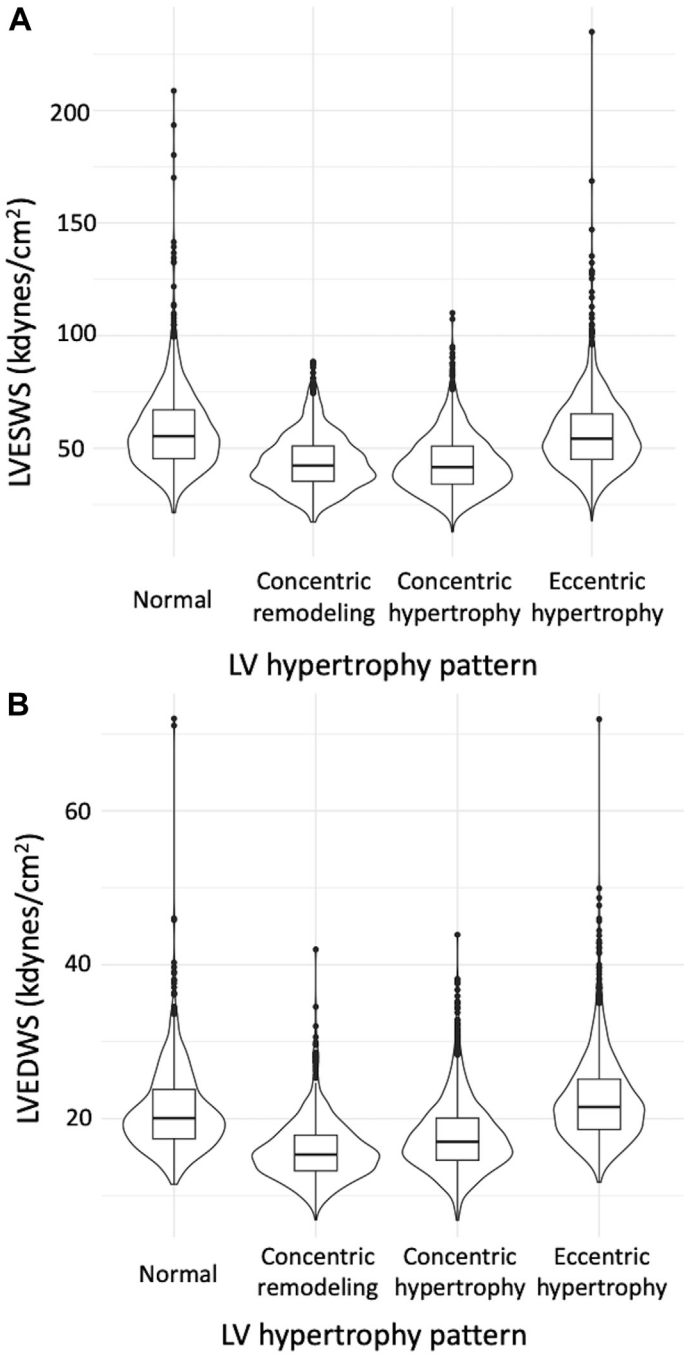
IVSd = interventricular septal wall thickness in diastole; LAVI = left atrial volume index; LVEDWS = left ventricular end diastolic wall stress; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVESWS = left ventricular end systolic wall stress; LVH = left ventricular hypertrophy; LVIDd = left ventricular internal diameter in diastole; PCWP = pulmonary capillary wedge pressure; PWTd = posterior wall thickness in diastole; RWT = relative wall thickness; TR peak vel = tricuspid regurgitation peak velocity.

associated with a composite endpoint of cardiovascular death, myocardial infarction, or stroke.[6] After adjustment for cardiovascular risk factors, however, LVESWS was associated with risk of myocardial infarction but not the composite endpoint. LVEDWS was not reported from the study. In ARIC study participants, we did not find LVESWS to be associated with risk of incident HF, while greater LVEDWS was. That the risk estimate between LVEDWS and incident HF did not attenuate when also accounting for all-cause death lends further support to the findings.

Prior investigations have also examined diastolic wall strain and incident HF risk. Like LVEDWS, diastolic wall strain can be calculated from echocardiographic data using wall thickness measures ([PWTs − PWTd]/PWTs).[21] This load-independent measure is thought to reflect intrinsic myocardial resistance to deformation with lower diastolic wall strain indicative of greater myocardial stiffness. In non-HF populations, lower diastolic wall strain has been associated with LV fibrosis, E/e', adverse cardiovascular outcomes, and death.[22-25] In the Jackson, MS subcohort of the ARIC study, which was comprised of adults of Black race, lower diastolic wall strain calculated from echocardiographic data obtained between 1993 and 1995 was associated with greater risk for incident HF before but not after adjustment for LVEF and mass index.[26] In contrast, in the broader and more contemporary ARIC cohort, we found LVEDWS to be associated with the risk of incident HF, independent of LVEF and mass index. The collective diastolic wall strain and LVEDWS data suggest LV loading conditions and chamber size are informative to understanding clinical HF development.

We also found variation in clinical correlates of LVEDWS and LVESWS. Older age, women, higher body mass index and systolic BP, as well as greater inflammation, as measured by circulating C-reactive protein levels, all significantly and independently associated with greater LVEDWS. This is a profile thought to be common among individuals with HF with preserved ejection fraction.[27] Within this cohort, in which the vast majority of LVEF values were within

FIGURE 2 LVESWS and LVEDWS According to Pattern of LV Hypertrophy



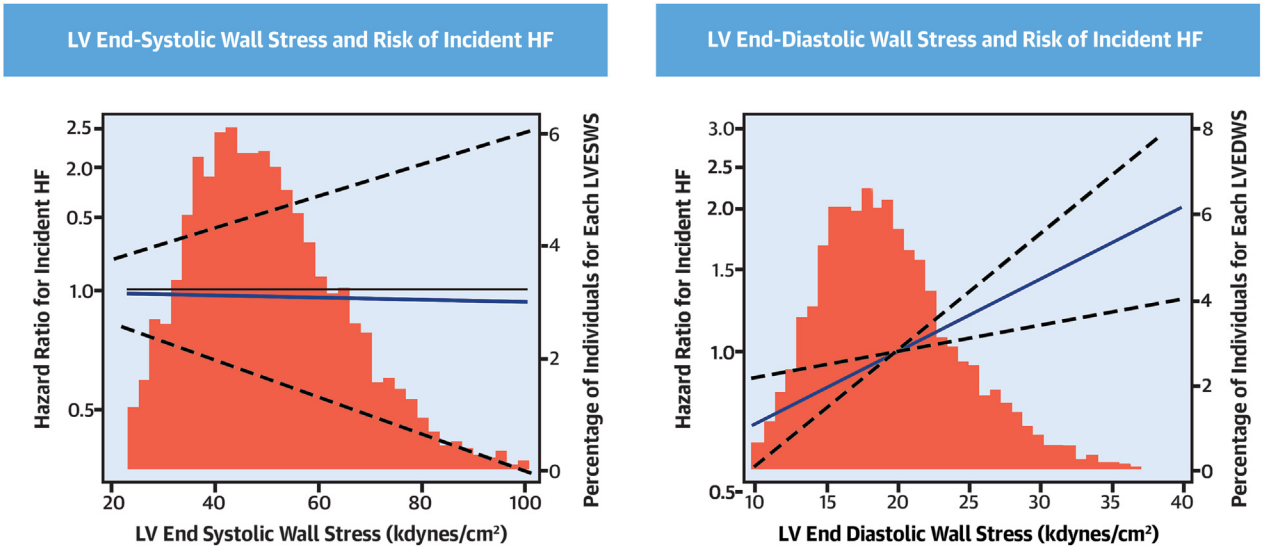
The distribution of LVESWS and LVEDWS in participants with normal LV geometry, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy are displayed in violin plots. Boxplots indicate the median and 25th-75th percentile of wall stress. Points indicate outliers. LV = left ventricle; LVEDWS = left ventricular end diastolic wall stress; LVESWS = left ventricular end systolic wall stress.

normal range, we found the expected inverse association between LVEF and wall stress, consistent with reports from others.[28-30] In ARIC, most individuals who developed incident HF had a measure of LVEF available at or near the time of HF diagnosis. LV ejection fraction was preserved in approximately half of these individuals. We did not find LVEDWS estimated by TTE at visit 5 differed between those who developed incident HF with preserved compared with reduced ejection fraction. These data suggest LVEDWS may be predictive of HF in general rather than specifically for HF with preserved or reduced ejection fraction. Our findings warrant further investigation of TTE-derived LVEDWS to inform earlier detection of subclinical cardiac remodeling. Insofar as body mass index, BP, and inflammation were the strongest modifiable correlates of greater LVEDWS, our findings may provide added emphasis on targeting these for the primary prevention of HF in elderly individuals.

We also found the association of LVEDWS and incident HF was not attenuated by adjustment for LV size or wall thickness, suggesting filling pressure was a relatively stronger contributor. Indeed, addition of E/e' to the model attenuated the significant association of LVEDWS with incident HF, while replacement of LVEDWS with E/e' revealed a similarly significant association with incident HF for E/e' independent of LV size or wall thickness. Insofar as E/e' is readily measured and clinically reported from echocardiographic studies, this could be utilized for assessing responses to strategies to prevent HF. We note the majority of values for E/e' in this cohort fell within a range of 8 to 12, which is not considered to be clearly elevated by current guidelines but likely reflect subclinical rise in filling pressure.

Strengths of our study include the large sample size, biracial community-based sample, core lab quantification of cardiac structure and function, and longitudinal follow-up for incident HF. Limitations should also be noted. The gold standard for quantification of wall stress involves invasive hemodynamic measures, such that TTE utilized in this analysis provides estimates of wall stress. Our results were similar regardless of formula for estimating PCWP from echocardiography. We appreciate the challenges with ascertaining HF from medical record review; however, the approach utilized in ARIC included adjudication by a committee using a standardized protocol that has been previously validated.[15] The majority of individuals in the cohort had a LVEF >50% at ARIC visit 5, such that our results may not be

CENTRAL ILLUSTRATION **Left Ventricular Wall Stress and Incident Heart Failure in Elderly Individuals**



White A, et al. JACC Adv. 2024;3(10):101262.

LV end systolic and diastolic wall stress (LVESWS, LVEDWS) were calculated at baseline among 4,601 ARIC study participants without prevalent HF. LVEDWS, but not LVESWS, was associated with the risk of incident heart failure over a median follow-up of 4.6 years. HR from Cox regression adjusted for LVEDWS, LVESWS, age, sex, race, history of hypertension, diabetes, coronary artery disease, atrial fibrillation, smoking status, pulse pressure, systolic blood pressure, body mass index, creatinine, glucose, C-reactive protein, troponin, NT-proBNP, triglycerides, LV ejection fraction, and LV mass. Reference values for HR calculations were (A) 0 kdynes/cm^2 and (B) 20 kdynes/cm^2. Solid line = HR; dashed line = 95% CI. Histogram displays percent of individuals according to wall stress. ARIC = Atherosclerosis Risk In Communities; HF = heart failure; LV = left ventricle; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

generalizable to individuals without prevalent HF but with lower LVEF. Future studies of sufficient sample size for the minority of individuals with asymptomatic LV dysfunction may be needed to better understand wall stress in this population. Our analysis focused on the correlates and prognostic significance of wall stress. We acknowledge that predictors of incident HF may differ between patients with HF with preserved and reduced ejection fraction, which was examined by Ho et al.[31] The observational nature of the study limits inferences regarding causation between wall stress and incident HF. Further, though we adjusted for traditional HF risk factors established biomarkers such as natriuretic peptides, troponin, and C-reactive protein, as well as LV mass index and ejection fraction, residual confounding cannot be excluded.

CONCLUSIONS

Among community-dwelling elderly individuals, greater LVEDWS was measured noninvasively with TTE associates with a higher risk for incident HF. Given the broad availability of TTE, noninvasive measurement of LVEDWS by TTE may be of utility as an intermediate marker of HF risk in elderly individuals and of potential use in physiologic studies and trials to understand the progression of LV remodeling and targets for preventive strategies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: LVEDWS can be noninvasively estimated from echocardiography, and higher levels are associated with greater risk of incident HF, independent of LVEF.

TRANSLATIONAL OUTLOOK 1: Targeting modifiable correlates of LVEDWS may inform primary prevention strategies for HF.

TRANSLATIONAL OUTLOOK 2: Serial noninvasive measurement of LV wall stress using echocardiography may be of utility in understanding the progression from LV remodeling to HF.

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KEY WORDS **cardiac function, echocardiogram, heart failure, left ventricular wall stress**