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ORIGINAL RESEARCH

# Associations of Left Ventricular Structure and Function With Blood Pressure in Heart Failure With Preserved Ejection Fraction: Analysis of the TOPCAT Trial

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**BACKGROUND:** Data on the association of systolic and diastolic blood pressure with the structure and function of failing hearts with preserved ejection fraction (EF) are sparse.

**METHODS AND RESULTS:** This analysis included 935 patients with heart failure (49.4% women; mean age, 69.9 years) with preserved EF (≥45%) enrolled in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) Trial before initiation of randomized therapy. Left ventricular (LV) structure (dimensions, wall thickness, and mass index), diastolic function (left atrial volume index, transmitral blood flow, and mitral annular velocities), and systolic function (EF and longitudinal strain) were assessed echocardiographically. In multivariable-adjusted analyses, association sizes expressed per 1-SD (14.8–mm Hg) increment in systolic blood pressure were 0.020 cm ($P$=0.003) and 0.018 cm ($P$=0.004) for LV septal and posterior wall thickness, respectively, and 2.42 mg/m$^2$ ($P$=0.018) for LV mass index. The corresponding associations with diastolic blood pressure were nonsignificant ($P$≥0.067). In similarly adjusted analyses, the association sizes expressed per 1-SD (10.7–mm Hg) increment in diastolic blood pressure were −0.15 for E/A ($P$<0.001), −0.76 for E/e′ ($P$=0.006), and −0.62% for EF ($P$=0.024). These findings were consistent, if models including systolic blood pressure were additionally adjusted for diastolic blood pressure and vice versa, albeit that the relation of EF with diastolic blood pressure weakened (−0.54%; $P$=0.10).

**CONCLUSIONS:** In diastolic heart failure, LV wall thickness and LV mass index increased with higher systolic blood pressure, but not with higher diastolic blood pressure, whereas functional measures reflecting diastolic LV function decreased with higher diastolic blood pressure, independent of systolic blood pressure. These observations highlight the importance of controlling both systolic and diastolic blood pressure as modifiable risk factors to reduce the risk of LV remodeling and diastolic LV dysfunction.

**Key Words:** blood pressure ■ diastolic heart failure ■ echocardiography ■ hypertension ■ left ventricle

Hypertension is the most important modifiable cardiovascular risk factor, as documented in numerous population studies,[1] patient cohorts,[2,3] and randomized clinical trials.[4] More than half a century ago, the Framingham investigators established that higher blood pressure increases cardiovascular complications.[5] Diastolic blood pressure drives the cardiovascular risk in young and middle-aged adults, whereas in older people, cardiovascular complications are more closely associated with the pulsatile

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## CLINICAL PERSPECTIVE

### What Is New?

- In patients with heart failure with preserved ejection fraction, low diastolic blood pressure is a forerunner of adverse cardiovascular events.
- However, to our knowledge, no previous study described how left ventricular structure and function in patients with heart failure with preserved ejection fraction are related to systolic and diastolic blood pressure.

### What Are the Clinical Implications?

- Our current study highlights the importance of controlling both systolic and diastolic blood pressure as modifiable risk factors to reduce the risk of left ventricular remodeling and diastolic left ventricular dysfunction in patients with heart failure with preserved ejection fraction or at risk of heart failure.
- Overtreatment with antihypertensive drugs to reduce left ventricular afterload and to improve the ejection fraction should be balanced against the risk of excessively lowering diastolic blood pressure, exposing the myocardium to ischemia and further functional deterioration.

### Nonstandard Abbreviation and Acronyms

| | |
|---|---|
| **e′peak** | peak early diastolic mitral annular tissue velocity |
| **E** | peak early diastolic transmitral flow velocity |
| **EF** | ejection fraction |
| **HFpEF** | heart failure with preserved ejection fraction |
| **LV** | left ventricular |

components of blood pressure, as exemplified by systolic blood pressure or pulse pressure.[6,7] Systolic hypertension increases the afterload against which the left ventricle (LV) has to operate.[8] Diastolic blood pressure sustains blood flow through the cardiac capillary network.[9,10] An excessively low diastolic blood pressure leads to reduced coronary blood flow[9] and subclinical myocardial damage.[10] Although the aforementioned observations are firmly established in populations and hypertensive patients,[1–7] in patients with heart failure with preserved ejection fraction (HFpEF), the risk associated with systolic and diastolic blood pressure might be different. HFpEF, also known as diastolic heart failure, represents ≈50% of all heart failure cases.[11] In HFpEF, low diastolic blood pressure is a forerunner of adverse cardiovascular events.[12,13] Shah and colleagues demonstrated that the echocardiographic phenotype of HFpEF is heterogeneous, but did not report on the association of the echocardiographic traits with blood pressure.[14] Furthermore, using as key words in title or abstract "blood pressure" AND "heart failure" combined with one of the following search terms, "echocardiograph*" OR "left ventricul*" OR "ejection fraction," a literature search did not reveal any previous study describing how LV structure and function in patients with HFpEF are related to systolic and diastolic blood pressure. We addressed this issue by analyzing the echocardiographic data obtained at baseline in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) Trial (NCT00094302).[15]

## METHODS

### Study Population

The TOPCAT Trial was an international, multicenter, randomized, double-blind, placebo-controlled trial.[15] The study was designed to investigate whether spironolactone improved clinical outcomes in patients with HFpEF compared with placebo. The TOPCAT Trial complied with the Declaration of Helsinki[16] and received ethical clearance. All patients signed informed consent before randomization. To obtain access to the TOPCAT Trial data, we first registered at the website of the Biologic Specimen and Data Repository Information Coordinating Center of National Heart, Lung, and Blood Institute (https://biolincc.nhlbi.nih.gov/). Next, we submitted a request for accessing the TOPCAT Trial data along with a protocol for the intended post hoc analysis and the approval by the ethics committee of the First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China. After we signed a Research Materials Distribution Agreement, National Heart, Lung, and Blood Institute transferred anonymized data. The requests to access the data set should be sent to the National Heart, Lung, and Blood Institute.

At 233 sites in 6 countries, 3445 patients with HFpEF were randomly assigned to spironolactone or placebo. Eligible patients were aged ≥50 years, had ≥1 sign, and had at least 1 symptom of heart failure with an ejection fraction (EF) not lower than 45%, controlled systolic blood pressure (defined as a systolic blood pressure of <140 or <160 mm Hg if the patient was on ≥3 antihypertensive drugs), and a serum potassium concentration level of <5.0 mmol/L. Of 3445 randomized patients with HFpEF, 935 (27.1%) underwent echocardiography before the initiation of randomized treatment[14] and were available for statistical analysis in the current study.

## Echocardiographic Measurement

At 27 of 270 TOPCAT Trial study sites, patients consented to participate in the echocardiographic substudy, which was performed according to the recommendations of the American Society of Echocardiography, as previously described.[14,17] Dedicated analysts read all study echocardiograms at the core laboratory at the Brigham and Women's Hospital, Boston, MA. The readers were blinded to clinical information and randomized assignment. Of the 935 analyzable imaging studies, complete 2-dimensional and Doppler data were available in 553 (59%), with all Doppler measures missing in 181 (19%) and tissue Doppler only missing in an additional 147 (16%) patients. Among the 78% of participants with Doppler measures, 76% were in sinus rhythm. Each measure was performed by the same analyst for all study participants. Intraobserver variability, performed in 60 studies, was as follows: wall thickness: coefficient of variation, 12%; bias, 0.02±0.1 cm; LV end-diastolic volume: coefficient of variation, 12%; bias, 1.6±10.5 mL; LV end-systolic volume: coefficient of variation, 18%; bias, 2.6±5.9 mL; LV EF: coefficient of variation, 6.6%; bias, 2.0±4.3%; peak early diastolic mitral annular tissue velocity (e′): coefficient of variation, 7.0%; bias, 0.1±0.4 cm/s; peak early diastolic transmitral flow velocity (E)/e′ ratio: coefficient of variation, 11%; bias, 0.2±1.2.[14,17]

In this study, we statistically analyzed LV structure, including LV dimensions, wall thickness, and mass index; diastolic function, including left atrial volume index, transmitral blood flow, and mitral annular tissue velocities; and systolic function, including EF and longitudinal strain.

In short, LV endocardial borders were manually traced at end diastole and end systole in the apical 4- and 2-chamber views, and LV volumes were derived according to the modified biplane Simpson rule.[18] In cases where the Simpson method could not be used because of missing or poor-quality apical views, the EF was calculated using the Teicholz method.[19] Given the low prevalence of regional wall motion abnormalities, LV mass was calculated by the American Society of Echocardiography recommended formula for estimation of LV mass from LV linear dimensions and indexed to body surface area.

Left atrial volume indexed to body surface area was assessed by the biplane area-length method from apical 2- and 4-chamber views at end systole.[18] The e′ value was measured from the septal and lateral sites of the mitral annulus. Mitral inflow velocity was assessed by pulsed wave Doppler from the apical 4-chamber view, by positioning the sample volume at the tip of the mitral leaflets. E/e′ ratio was calculated as E wave divided by e′. LV longitudinal strain was assessed by 2-dimensional speckle-tracking echocardiography.

## Other Measurements

Patients who participated in the TOPCAT Trial underwent a detailed baseline evaluation. Blood pressure was measured manually in 75.6% of participants and by automated techniques in 24.4%. Body mass index was weight in kilograms divided by the height squared in meters. Study nurses also administered a standardized questionnaire inquiring into each participant's medical history, smoking habits, and intake of medications.

## Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.4 (SAS Institute Inc, Cary, NC), maintenance level 5. We applied the Kolmogorov-Smirnov test for assessing the normality of distributions. For between-group comparison of means and proportions, we applied the large-sample z-test and Fisher exact test, respectively. For ease of interpretation, we used the absolute value of the longitudinal strain measurements, which were all negative. Significance was a 2-sided α level of ≤0.05.

In unadjusted and multivariable-adjusted linear regression analyses, we expressed the association sizes of the echocardiographic indexes with blood pressure for a 1-SD increment in systolic or diastolic blood pressure. In multivariable-adjusted analyses, in line with previous TOPCAT Trial publications,[14,17] we accounted for sex, age, ethnicity, body mass index, heart rate, current smoking, dyslipidemia, diabetes mellitus, use of antihypertensive medications by drug class (ie, diuretics, β blockers, inhibitors of the renin-angiotensin system [angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers], and calcium channel blockers), and intake of aspirin, lipid-lowering drugs, other cardiovascular medications, and antidiabetic agents. Missing values in the independent variables body mass index (n=2) and blood pressure (n=1) were replaced by their respective means. Missing values in the dependent variables (LV structure and function) were not imputed. In unadjusted and multivariable-adjusted models that included both systolic and diastolic blood pressure, we computed the variance inflation factor to assess to what extent parameter estimates for systolic and diastolic blood pressure levels were affected by collinearity. We examined whether the association of the echocardiographic indexes with blood pressure differed by subgroups by introducing the interactions of either systolic or diastolic blood pressure with sex, ethnicity, and age.

**Table 1. Characteristics of Participants by Median of Systolic and Diastolic Blood Pressure**

| Characteristics | Systolic Blood Pressure | | | Diastolic Blood Pressure | | |
|---|---|---|---|---|---|---|
| | <130 mm Hg | ≥130 mm Hg | *P* Value | <75 mm Hg | ≥75 mm Hg | *P* Value |
| No. (%) with characteristic | 426 (45.6) | 509 (54.4) | | 460 (49.2) | 475 (50.8) | |
| Women | 191 (44.8) | 271 (53.2) | 0.010 | 225 (48.9) | 237 (49.9) | 0.76 |
| Race | | | | | | |
| White | 358 (84.0) | 412 (80.9) | 0.22 | 367 (79.8) | 403 (84.8) | 0.042 |
| Black | 56 (13.2) | 71 (14.0) | 0.72 | 71 (15.4) | 56 (11.8) | 0.10 |
| Others | 12 (2.8) | 26 (5.1) | 0.025 | 22 (4.8) | 16 (3.4) | 0.52 |
| Current smoking | 45 (10.6) | 36 (7.1) | 0.060 | 32 (7.0) | 49 (10.3) | 0.070 |
| NYHA class III or IV | 153 (36.2) | 190 (37.3) | 0.72 | 179 (39.1) | 164 (34.6) | 0.16 |
| Hypertension | 370 (86.8) | 484 (95.3) | <0.001 | 413 (90.0) | 441 (92.8) | 0.12 |
| Diabetes mellitus | 158 (37.1) | 215 (42.3) | 0.10 | 212 (46.2) | 161 (33.9) | <0.001 |
| Dyslipidemia | 294 (69.0) | 345 (67.9) | 0.72 | 336 (73.2) | 303 (63.8) | 0.002 |
| eGFR <60 mL/min per 1.73 $m^2$ | 175 (41.1) | 225 (44.2) | 0.34 | 229 (49.8) | 171 (36.0) | <0.001 |
| Medications | | | | | | |
| β Blockers | 347 (81.5) | 394 (77.4) | 0.13 | 377 (82.0) | 364 (76.6) | 0.045 |
| Diuretic | 351 (82.4) | 429 (84.3) | 0.44 | 397 (86.3) | 383 (80.6) | 0.020 |
| Inhibitors of the renin system | 321 (75.4) | 435 (85.5) | <0.001 | 350 (76.1) | 406 (85.5) | <0.001 |
| Calcium channel blocker | 129 (30.3) | 230 (45.2) | <0.001 | 179 (38.9) | 180 (37.9) | 0.75 |
| Antidiabetic agent | 143 (33.6) | 191 (37.5) | 0.21 | 200 (43.5) | 134 (28.2) | <0.001 |
| Other cardiovascular medication | 406 (95.3) | 465 (91.4) | 0.017 | 441 (95.9) | 430 (90.5) | 0.001 |
| Mean±SD of characteristic | | | | | | |
| Age, y | 70.1±9.9 | 69.7±9.5 | 0.54 | 72.3±9.5 | 67.6±9.3 | <0.001 |
| Body mass index, kg/$m^2$ | 32.5±7.5 | 32.7±7.2 | 0.72 | 33.1±8.1 | 32.1±6.5 | 0.034 |
| Systolic blood pressure, mm Hg | 115.3±9.4 | 138.9±8.5 | <0.001 | 122.0±15.4 | 134.0±11.4 | <0.001 |
| Diastolic blood pressure, mm Hg | 68.4±9.9 | 77.8±9.5 | <0.001 | 64.5±6.7 | 82.3±5.1 | <0.001 |
| Heart rate, beats/min | 68.9±11.7 | 69.1±11.1 | 0.78 | 67.4±11.5 | 70.6±11.0 | <0.001 |
| eGFR, mL/min per 1.73 $m^2$ | 66.6±24.2 | 66.2±19.2 | 0.78 | 62.8±20.4 | 70.0±22.2 | <0.001 |

eGFR was calculated according to the 4-component MDRD (Modification of Diet in Renal Disease) study prediction equation. Inhibitors of the renin-angiotensin system include angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers. *P* values denote the significance of the between-group differences. eGFR indicates estimated glomerular filtration rate (estimated from serum creatinine); and NYHA, New York Heart Association.

# RESULTS

## Characteristics of Participants

The 935 patients with HFpEF included 462 (49.4%) women and were predominantly white (82.4%). Mean±SD values in all patients were 69.9±9.7 years for age, 32.6±7.3 kg/$m^2$ for body mass index, and 128.1±14.8/73.6±10.7 mm Hg for systolic/diastolic blood pressure.

Table 1 lists the characteristics of participants by median of systolic or diastolic blood pressure. Patients in the high compared with the low systolic blood pressure group were more likely to be women, had higher prevalence of hypertension, and more frequently used inhibitors of the renin system and calcium channel blockers. Participants in the high compared with the low diastolic blood pressure group were more likely to be white and had a lower prevalence of diabetes mellitus and dyslipidemia; they used fewer antidiabetic drugs, β blockers, and diuretics, but more inhibitors of the renin system (P≤0.045).

Women compared with men had smaller (*P*<0.001) LV end-diastolic and end-systolic volumes, septal and

**Table 2. Baseline Cardiac Structure and Function**

| Characteristics | Women | | Men | | All | |
|---|---|---|---|---|---|---|
| | No. | Mean±SD | No. | Mean±SD | No. | Mean±SD |
| LV structure | | | | | | |
| LV end-diastolic volume index, mL/m$^2$ | 429 | 46.2±14.3 | 433 | 53.6±15.7‡ | 862 | 49.9±15.5 |
| LV end-systolic volume index, mL/m$^2$ | 429 | 18.4±8.4 | 433 | 23.0±10.5‡ | 862 | 20.7±9.8 |
| LV end-diastolic dimension, cm | 431 | 4.61±0.51 | 447 | 4.99±0.58‡ | 878 | 4.80±0.58 |
| LV end-systolic dimension, cm | 431 | 3.19±0.44 | 447 | 3.54±0.52‡ | 878 | 3.36±0.51 |
| Septal wall thickness, cm | 431 | 1.14±0.19 | 447 | 1.26±0.21‡ | 878 | 1.20±0.21 |
| Posterior wall thickness, cm | 431 | 1.11±0.18 | 446 | 1.21±0.20‡ | 877 | 1.16±0.20 |
| LV mass index, mg/m$^2$ | 429 | 102.8±29.2 | 446 | 116.3±30.6‡ | 875 | 109.7±30.7 |
| Relative wall thickness | 431 | 0.49±0.10 | 446 | 0.49±0.11 | 877 | 0.49±0.10 |
| LV diastolic function | | | | | | |
| E/A ratio | 301 | 1.20±0.68 | 249 | 1.29±0.68 | 550 | 1.24±0.68 |
| TDI e′ (lateral), cm/s | 269 | 7.93±3.36 | 234 | 8.53±3.1* | 503 | 8.21±3.3 |
| TDI e′ (septal), cm/s | 257 | 5.95±2.32 | 254 | 6.31±2.2 | 511 | 6.13±2.2 |
| E/e′ (lateral) | 267 | 12.3±6.1 | 226 | 11.3±5.6 | 493 | 11.8±5.9 |
| E/e′ (septal) | 254 | 15.9±6.7 | 245 | 15.4±7.0 | 499 | 15.6±6.8 |
| Left atrial volume index, mL/m$^2$ | 420 | 29.6±12.1 | 414 | 29.9±12.9 | 834 | 29.8±12.5 |
| LV systolic function | | | | | | |
| Ejection fraction, % | 462 | 60.6±7.3 | 473 | 58.0±8.2‡ | 935 | 59.3±7.9 |
| Longitudinal strain, % | 240 | 16.0±3.5 | 207 | 15.0±3.4† | 447 | 15.6±3.5 |

Longitudinal strain is a negative value, but for ease of interpretation, the absolute value was reported. e′ indicates peak early diastolic mitral annular tissue velocity; E, peak early diastolic transmitral flow velocity; E/A ratio, the ratio of peak early (E) to late (A) diastolic velocities; LV, left ventricular; and TDI, tissue Doppler imaging.

Significance of the sex difference: *$P$≤0.05, †$P$≤0.01, and ‡$P$≤0.001.

posterior wall thickness, and LV mass index, but higher ($P$≤0.002) EF and longitudinal strain (Table 2).

## Association of LV Structure With Blood Pressure

In unadjusted analyses (Table 3), the septal and posterior wall thickness and the LV mass index increased with systolic blood pressure. The corresponding associations with diastolic blood pressure were nonsignificant ($P$≥0.47). Adjustment for diastolic blood pressure did not remove the significance of the associations with systolic blood pressure.

With adjustments applied for sex, age, ethnicity, body mass index, heart rate, current smoking, dyslipidemia, diabetes mellitus, use of antihypertensive medications by drug class, and intake of aspirin, lipid-lowering drugs, other cardiovascular medications, and antidiabetic agents, the association sizes with systolic blood pressure were 0.020 cm ($P$=0.003) and 0.018 cm ($P$=0.004) for septal and posterior thickness, respectively, and 2.42 mg/m$^2$ ($P$=0.018) for LV mass index. Additional adjustment for diastolic blood pressure produced confirmatory results (Figure).

## Association of LV Function With Blood Pressure

In unadjusted analyses (Table 3), E/A, E/e′, and left atrial volume index decreased with higher diastolic blood pressure with association sizes per 1-SD (10.7–mm Hg) increment in diastolic blood pressure. Conversely, the EF and longitudinal strain decreased with higher diastolic blood pressure. Adjustment for systolic blood pressure did not remove the significance of the associations with diastolic blood pressure, except for left atrial volume index ($P$=0.088).

In multivariable-adjusted models, the association sizes with diastolic blood pressure were −0.15 for E/A ($P$<0.001), −0.76 for E/e′ ($P$=0.006), and −0.62% for EF ($P$=0.024). With additional adjustment for systolic blood pressure, the corresponding association sizes were −0.15 for E/A ($P$<0.001), −0.91 for E/e′ ($P$=0.005), and −0.54% for EF ($P$=0.10). In all models including both systolic and diastolic blood pressure, the variance inflation factor was ≤1.72.

## Sensitivity Analysis

In multivariable-adjusted models relating diastolic dysfunction to diastolic blood pressure, we additionally

**Table 3. Cardiac Structure and Function in Relation to Blood Pressure at Baseline**

| Blood Pressure Model | Models Including SBP or DBP | | Models Including SBP and DBP | |
|---|---|---|---|---|
| | SBP | DBP | SBP | DBP |
| Unadjusted | | | | |
| Septal wall thickness, cm | 0.022 (0.008 to 0.036)† | 0.005 (−0.009 to 0.019) | 0.026 (0.010 to 0.042)† | −0.009 (−0.025 to 0.008) |
| Posterior wall thickness, cm | 0.020 (0.007 to 0.033)† | 0.003 (−0.010 to 0.016) | 0.025 (0.010 to 0.040)† | −0.009 (−0.024 to 0.006) |
| LV mass index, mg/m$^2$ | 2.46 (0.45 to 4.46)* | 0.021 (−2.00 to 2.05) | 3.33 (0.99 to 5.66)† | −1.70 (−4.06 to 0.65) |
| Relative wall thickness | 0.007 (0.0004 to 0.014)* | 0.004 (−0.003 to 0.010) | 0.007 (−0.0007 to 0.015) | −0.00001 (−0.008 to 0.008) |
| E/A ratio | −0.056 (−0.11 to −0.0002)* | −0.16 (−0.22 to −0.11)‡ | 0.026 (−0.035 to 0.088) | −0.18 (−0.24 to −0.11)‡ |
| TDI e′, cm/s | −0.11 (−0.32 to 0.11) | 0.003 (−0.22 to 0.23) | −0.14 (−0.39 to 0.10) | 0.076 (−0.18 to 0.33) |
| E/e′ | −0.009 (−0.50 to 0.48) | −1.10 (−1.61 to −0.60)‡ | 0.65 (0.11 to 1.20)* | −1.44 (−2.01 to −0.86)‡ |
| LA volume index, mL/m$^2$ | −0.78 (−1.62 to 0.058) | −1.05 (−1.90 to −0.19)* | −0.35 (−1.32 to 0.62) | −0.86 (−1.86 to 0.13) |
| Ejection fraction, % | −0.13 (−0.64 to 0.38) | −0.93 (−1.43 to −0.43)‡ | 0.48 (−0.11 to 1.07) | −1.18 (−1.77 to −0.59)‡ |
| Longitudinal strain, % | 0.20 (−0.12 to 0.52) | −0.32 (−0.64 to 0.0004)* | 0.48 (0.12 to 0.86)† | −0.57 (−0.94 to −0.20)† |
| Adjusted | | | | |
| Septal wall thickness, cm | 0.020 (0.007 to 0.033)† | 0.013 (−0.0009 to 0.027) | 0.019 (0.003 to 0.035)* | 0.002 (−0.015 to 0.019) |
| Posterior wall thickness, cm | 0.018 (0.006 to 0.030)† | 0.012 (−0.001 to 0.025) | 0.017 (0.002 to 0.032)* | 0.002 (−0.014 to 0.018) |
| LV mass index, mg/m$^2$ | 2.42 (0.41 to 4.43)* | 1.03 (−1.11 to 3.16) | 2.71 (0.30 to 5.12)* | −0.56 (−3.12 to 2.00) |
| Relative wall thickness | 0.005 (−0.001 to 0.012) | 0.007 (−0.0002 to 0.014) | 0.002 (−0.006 to 0.011) | 0.006 (−0.003 to 0.014) |
| E/A ratio | −0.069 (−0.13 to −0.013)* | −0.15 (−0.21 to −0.091)‡ | 0.006 (−0.059 to 0.071) | −0.15 (−0.22 to −0.083)‡ |
| TDI e′, cm/s | −0.090 (−0.31 to 0.13) | −0.060 (−0.31 to 0.19) | −0.086 (−0.35 to 0.18) | −0.010 (−0.30 to 0.28) |
| E/e′ | −0.17 (−0.67 to 0.32) | −0.76 (−1.30 to −0.22)† | 0.27 (−0.31 to 0.85) | −0.91 (−1.55 to −0.28)† |
| LA volume index, mL/m$^2$ | −0.62 (−1.46 to 0.22) | −0.038 (−0.94 to 0.86) | −0.86 (−1.87 to 0.14) | 0.47 (−0.61 to 1.55) |
| Ejection fraction, % | −0.41 (−0.92 to 0.098) | −0.62 (−1.16 to −0.081)* | −0.13 (−0.74 to 0.48) | −0.54 (−1.19 to 0.10) |
| Longitudinal strain, % | 0.051 (−0.28 to 0.38) | −0.32 (−0.66 to 0.024) | 0.30 (−0.090 to 0.68) | −0.48 (−0.88 to −0.079)* |

Effect sizes (95% CIs) express the changes in the echocardiographic traits associated with a 1-SD increase in SBP and DBP. Adjusted estimates account for sex, age, ethnicity, body mass index, heart rate, current smoking, dyslipidemia, diabetes mellitus, use of antihypertensive medications by drug class (ie, diuretics, β blockers, inhibitors of the renin-angiotensin system, and calcium channel blockers), and intake of aspirin, lipid-lowering drugs, other cardiovascular medications, and antidiabetic agents. In all models, the variance inflation factor for collinearity between SBP and DBP was ≤1.72. Longitudinal strain is a negative value, but for ease of interpretation, longitudinal strain was expressed as an absolute value. DBP indicates diastolic blood pressure; e′, peak early diastolic mitral annular tissue velocity; E, peak early diastolic transmitral flow velocity; E/A ratio, the ratio of peak early (E) to late (A) diastolic velocities; LA, left atrial; LV, left ventricular; SBP, systolic blood pressure; and TDI, tissue Doppler imaging.

Significance of the associations: *$P$≤0.05, †$P$≤0.01, and ‡$P$≤0.001.

adjusted for longitudinal strain, which produced confirmatory results. The same was true when models relating longitudinal strain to diastolic blood pressure were additionally adjusted for E/e′.

Sensitivity analyses of LV structure and function related to blood pressure in various subgroups delineated by sex (Tables S1 and S2), ethnicity (whites versus nonwhites; Table S3), and median of age (Table S4) generated confirmatory results. Introducing an interaction term of systolic or diastolic blood pressure with sex ($P$≥0.25), ethnicity ($P$≥0.051), or age ($P$≥0.053) into multivariable-adjusted models relating indexes of LV structure and diastolic dysfunction to blood pressure produced results similar to those reported in Table 3. However, the interaction of ethnicity was significant for septal ($P$≤0.025) and posterior thickness ($P$≤0.003) with systolic and diastolic blood pressure and for E/A ($P$=0.043) with diastolic blood pressure. The interaction of age was significant for septal ($P$=0.002) and posterior thickness ($P$<0.001), LV mass index ($P$<0.001), and E/e′ ($P$=0.024) with systolic blood pressure and for left atrial volume index ($P$=0.046) with diastolic blood pressure.

## DISCUSSION

In the current study, we examined the association of LV structure and function with systolic and diastolic blood pressure in patients with HFpEF. The key findings of our study can be summarized as follows: (1) in patient with HFpEF, even with multiple adjustments applied, LV wall thickness and LV mass index increased with higher systolic blood pressure, independent of diastolic blood pressure; and (2) the functional measures reflecting LV diastolic function were inversely associated with higher diastolic blood pressure, independent of systolic blood pressure.

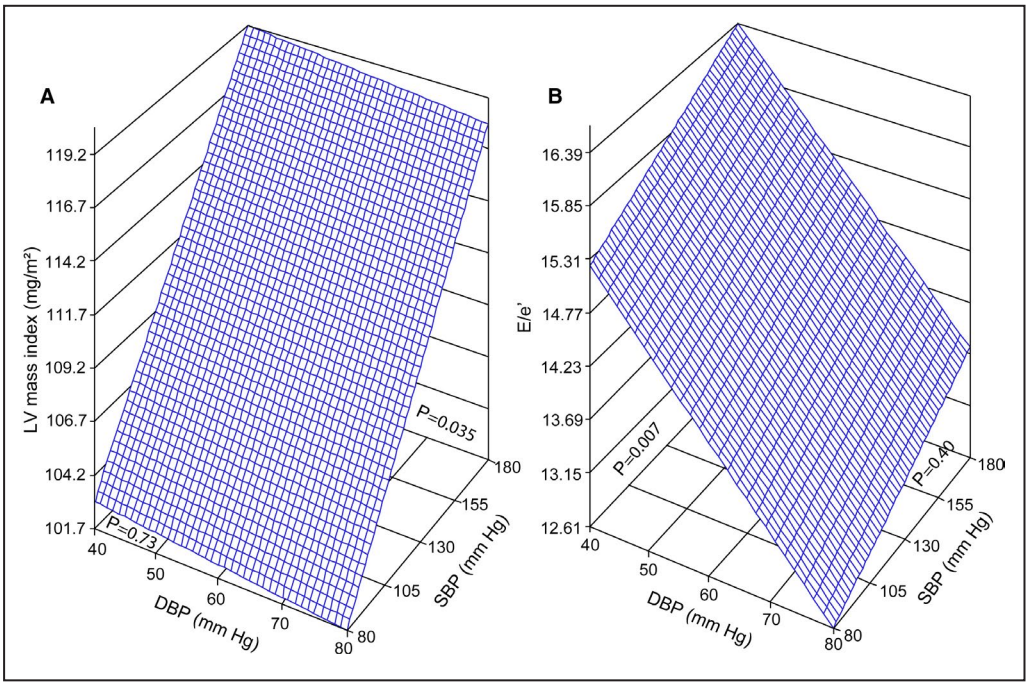


**Figure. Multivariable-adjusted associations of the left ventricular (LV) mass index (A) and E wave/peak early diastolic tissue velocity (E/e') (B) with systolic (SBP) and diastolic (DBP) blood pressure in patients with heart failure with preserved ejection fraction.**
The plane shows the independent associations of LV mass index and E/e′ with SBP and DBP. The plotted plane was standardized to the mean distribution in the whole study patients of sex, age, ethnicity, body mass index, heart rate, current smoking, dyslipidemia, diabetes mellitus, use of antihypertensive medications by drug class (ie, diuretics, β blockers, inhibitors of the renin-angiotensin system, and calcium channel blockers), and intake of aspirin, lipid-lowering drugs, other cardiovascular medications, and antidiabetic agents.

The literature describes several pathophysiological mechanisms potentially underlying the differential association of cardiac structure and function with systolic and diastolic blood pressure.[20] First, the pathophysiological characteristics of HFpEF include not only diastolic function but also impaired ventricular-vascular coupling and an excessive peripheral vasodilation.[21] A low systolic blood pressure in HFpEF is part of the syndrome and a hallmark indicative of a more severely ill patient population. The same applies to the low stroke volume, which may reflect concentric LV remodeling and LV hypertrophy, resulting in a disproportionally small and stiff LV. Antihypertensive therapy may reduce arterial and ventricular stiffness, enhance ventricular-arterial coupling, and improve systolic and diastolic LV function.[22] Furthermore, a low diastolic blood pressure can result in decreased coronary perfusion pressure, leading to further myocardial damage and worsening LV dysfunction.[10]

Our current findings might explain previously reported outcome studies relating adverse health outcomes to systolic or diastolic blood pressure. In TOPCAT Trial patients, there was no association between adverse health outcomes and systolic blood pressure at enrollment.[23] In contrast, in 10 535 patients with heart failure and reduced EF enrolled in the Medicare-linked OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry, a systolic blood pressure of <130 mm Hg predicted all-cause mortality and rehospitalization for any cause or for heart failure.[24] The hazard ratios amounted to 1.32 (95% CI, 1.15–1.53), 1.11 (95% CI, 1.01–1.23), and 1.24 (95% CI, 1.09–1.42), respectively.[24] Among 3471 TOPCAT Trial patients followed up for 3.0 years, 881 experienced a primary outcome event.[12] Compared with patients with a diastolic blood pressure of 80 to 89 mm Hg, the adjusted hazard ratios in patients with diastolic blood pressure <60 mm Hg were 1.65 (95% CI, 1.29–2.11) for the primary outcome and 1.89 (95% CI, 1.37–2.61) for all-cause mortality.[12] The association between hospitalization for heart failure and diastolic blood pressure was linear, whereas the association of death and cardiovascular death was nonlinear, with a greater risk of death if diastolic

blood pressure was <60 mm Hg or ≥90 mm Hg.[13] In line with these findings, our current findings demonstrated that the functional measures reflecting LV diastolic function were inversely associated with higher diastolic blood pressure. Furthermore, patients with HFpEF usually have clinical or subclinical LV systolic dysfunction, as assessed with LV global strain.[25] In multivariable-adjusted models relating diastolic dysfunction to diastolic blood pressure, we additionally adjusted for longitudinal strain, which produced confirmatory results. The same was true when models relating longitudinal strain to diastolic blood pressure were additionally adjusted for E/e′. Of note, increased afterload is well known to reduce longitudinal strain in the general population[25,26] and in individuals with stage A subclinical heart failure.[25] Our study also indicates that higher diastolic blood pressure was associated with a decline in longitudinal strain in patients with preserved systolic function.

Similar mechanisms as currently described might also be at play in the early stages of LV dysfunction. Indeed, heart failure is a progressive condition that begins with risk factors for LV dysfunction (eg, hypertension), proceeds to asymptomatic changes in cardiac structure (eg, LV hypertrophy) and function (eg, impaired LV relaxation), and then evolves into clinically overt heart failure, disability, and death.[27] The 5-year mortality rate of symptomatic heart failure is ≈60%.[28] Diastolic heart failure is characterized by slow LV relaxation, increased LV stiffness, increased interstitial deposition of collagen, and modified extracellular matrix proteins.[21] Diastolic heart failure accounts for 40% to 50% of all heart failure cases and has a prognosis as ominous as systolic heart failure.[21] In randomly recruited European population samples, the frequency of asymptomatic echocardiographically diagnosed diastolic LV dysfunction (early stage) is as high as 27%,[29,30] with a 5-year progression rate of 10%,[31] resulting in 22.5 hospitalization days per 1000 citizens (http://www.ehnheart.org; 2017). Over a 5- to 8-year horizon, both diastolic[32] and systolic[33] LV dysfunction predict the incidence of cardiovascular complications. Along similar lines, electrocardiographic[34] and echocardiographic[35] LV hypertrophy predict fatal and nonfatal cardiovascular outcomes.

## Strengths and Limitations

To the best of our knowledge, our study is the first to report on the association of cardiac structure and function with both systolic and diastolic levels in patients with HFpEF. We checked whether our multivariable-adjusted models including both blood pressure components were vulnerable to problems caused by collinearity. However, the variance inflation factor between systolic and diastolic blood pressure levels did not exceed 1.72. On the other hand, our study must also be interpreted within the context of its limitations. First, the present study had a cross-sectional design, which precludes direct causal inference. Second, not all patients randomized into the TOPCAT Trial underwent echocardiography at baseline. Compared with TOPCAT Trial participants not included in the echocardiographic study, those included differed in some baseline characteristics, which, although relatively minor, may limit the generalizability of these findings.[12,13] Patients with a baseline echocardiogram were on average 1.80 years older ($P<0.001$) and had a slightly higher body mass index (0.71 kg/m$^2$; $P=0.009$). However, participants with and without baseline echocardiogram had a similar heart rate and included proportionally a similar number of women, hypertensive patients, and smokers ($P\geq0.093$). Third, we acknowledge that the main aim of the TOPCAT Trial was not to determine the role of blood pressure in patients with HFpEF and that future studies including clinical trials of blood pressure targets in HFpEF may be warranted. Finally, as the current analysis was retrospective, the number of echocardiographic traits available for analysis differed across the study population, with fewer measurements being available for cardiac function than structure. However, body mass index was similar in patients with and without missing echocardiographic traits, suggesting that missingness was not related to the obesity of the patients.

## Perspective

From a clinical point of view, our current study highlights the importance of controlling both systolic and diastolic blood pressure as modifiable risk factors to reduce the risk of LV remodeling and diastolic LV dysfunction in patients at risk of diastolic LV dysfunction or with overt HFpEF. Overtreatment with antihypertensive drugs to reduce LV afterload and to improve the EF should be balanced against the risk of excessively lowering diastolic blood pressure, exposing the myocardium to ischemia and further functional deterioration.[10]

## ARTICLE INFORMATION

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## Disclosures

None.

## Supplementary Materials

**Tables S1–S4**

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# SUPPLEMENTAL MATERIAL

**Table S1. Cardiac Structure and Function in Relation to Blood Pressure at Baseline in Men.**

| Blood Pressure Model | Models Including a Single BP | | Models Including Two BP | |
|---|---|---|---|---|
| | SBP | DBP | SBP | DBP |
| Unadjusted | | | | |
| Septal wall thickness, cm | 0.024 (0.004 to 0.044)* | 0.008 (-0.012 to 0.028) | 0.028 (0.005 to 0.051)* | -0.007 (-0.030 to 0.016) |
| Posterior wall thickness, cm | 0.029 (0.011 to 0.048)† | 0.009 (-0.009 to 0.027) | 0.034 (0.013 to 0.056)† | -0.010 (-0.031 to 0.012) |
| LV mass index, mg/m$^2$ | 2.26 (-0.58 to 5.09) | 0.70 (-2.13 to 3.53) | 2.65 (-0.72 to 6.02) | -0.72 (-4.08 to 2.63) |
| Relative wall thickness | 0.011 (0.001 to 0.021)* | 0.006 (-0.004 to 0.016) | 0.011 (-0.0003 to 0.023) | -0.0005 (-0.012 to 0.011) |
| E/A ratio | -0.056 (-0.14 to 0.028) | -0.17 (-0.26 to -0.10)‡ | 0.044 (-0.052 to 0.14) | -0.20 (-0.29 to -0.10)‡ |
| TDI e', cm/s | -0.16 (-0.45 to 0.13) | -0.009 (-0.32 to 0.30) | -0.22 (-0.56 to 0.13) | 0.11 (-0.25 to 0.48) |
| E/e' | -0.042 (-0.75 to 0.67) | -1.20 (-1.94 to -0.46)† | 0.76 (-0.054 to 1.58) | -1.62 (-2.48 to -0.76)‡ |
| LA volume index, mL/m$^2$ | -0.31 (-1.53 to 0.90) | -1.00 (-2.26 to 0.26) | 0.29 (-1.15 to 1.73) | -1.16 (-2.66 to 0.33) |
| Ejection fraction, % | -0.56 (-1.30 to 0.18) | -1.23 (-1.97 to -0.49)† | 0.14 (-0.73 to 1.02) | -1.31 (-2.18 to -0.43)† |
| Longitudinal strain, % | -0.098 (-0.56 to 0.37) | -0.62 (-1.08 to -0.15)† | 0.35 (-0.20 to 0.90) | -0.81 (-1.37 to -0.26)† |
| Adjusted | | | | |
| Septal wall thickness, cm | 0.016 (-0.004 to 0.035) | 0.018 (-0.003 to 0.039) | 0.010 (-0.015 to 0.033) | 0.013 (-0.013 to 0.039) |
| Posterior wall thickness, cm | 0.022 (0.004 to 0.041)* | 0.023 (0.003 to 0.042)* | 0.015 (-0.007 to 0.038) | 0.013 (-0.011 to 0.037) |
| LV mass index, mg/m$^2$ | 1.65 (-1.27 to 4.56) | 1.89 (-1.23 to 5.02) | 0.94 (-2.63 to 4.51) | 1.31 (-2.53 to 5.15) |
| Relative wall thickness | 0.009 (-0.001 to 0.020) | 0.012 (0.002 to 0.023)* | 0.004 (-0.008 to 0.016) | 0.010 (-0.003 to 0.023) |
| E/A ratio | -0.082 (-0.17 to 0.002) | -0.14 (-0.23 to -0.046)† | -0.011 (-0.11 to 0.094) | -0.13 (-0.24 to -0.016)* |
| TDI e', cm/s | -0.18 (-0.48 to 0.13) | -0.036 (-0.38 to 0.31) | -0.24 (-0.61 to 0.14) | 0.12 (-0.30 to 0.54) |
| E/e' | -0.18 (-0.89 to 0.52) | -0.64 (-1.43 to 0.15) | 0.23 (-0.64 to 1.09) | -0.79 (-1.77 to 0.18) |
| LA volume index, mL/m$^2$ | -0.38 (-1.60 to 0.85) | -0.33 (-1.70 to 1.04) | -0.31 (-1.83 to 1.20) | -0.13 (-1.82 to 1.57) |
| Ejection fraction, % | -0.76 (-1.52 to 0.002) | -0.87 (-1.69 to -0.054)* | -0.44 (-1.36 to 0.49) | -0.60 (-1.61 to 0.40) |
| Longitudinal strain, % | -0.19 (-0.69 to 0.30) | -0.61 (-1.13 to -0.090)* | 0.21 (-0.39 to 0.82) | -0.74 (-1.38 to -0.10)* |

Effect sizes (95% confidence interval) express the changes in the echocardiographic traits associated with a 1-SD increase in systolic (SBP) and diastolic (DBP) blood pressure. Adjusted estimates account for sex, age, ethnicity, body mass index, heart rate, current smoking, dyslipidemia, diabetes mellitus, use of antihypertensive medications by drug class i.e., diuretics, β-blocker, inhibitors of the renin-angiotensin, calcium-channel blockers, and intake of aspirin, lipid-lowering drugs, other cardiovascular medications, and antidiabetic agents. Longitudinal strain is a negative value, but for ease of interpretation longitudinal strain was expressed as an absolute value. Significance of the associations: * $P \leq 0.05$, † $P \leq 0.01$, and ‡ $P \leq 0.001$.

**Table S2. Cardiac Structure and Function in Relation to Blood Pressure at Baseline in Women.**

| Blood Pressure Model | Models Including a Single BP | | Models Including Two BP | |
|---|---|---|---|---|
| | SBP | DBP | SBP | DBP |
| Unadjusted | | | | |
| Septal wall thickness, cm | 0.031 (0.013 to 0.049)‡ | 0.006 (-0.012 to 0.024) | 0.037 (0.017 to 0.057)‡ | -0.013 (-0.033 to 0.008) |
| Posterior wall thickness, cm | 0.021 (0.004 to 0.037)* | 0.001 (-0.016 to 0.018) | 0.027 (0.007 to 0.046)† | -0.012 (-0.032 to 0.007) |
| LV mass index, mg/m$^2$ | 3.96 (1.26 to 6.65)† | -0.20 (-2.97 to 2.57) | 5.35 (2.26 to 8.44)‡ | -2.88 (-6.02 to 0.26) |
| Relative wall thickness | 0.004 (-0.005 to 0.013) | 0.002 (-0.008 to 0.011) | 0.004 (-0.006 to 0.015) | -0.0003 (-0.011 to 0.010) |
| E/A ratio | -0.049 (-0.12 to 0.026) | -0.16 (-0.23 to -0.082)‡ | 0.023 (-0.059 to 0.10) | -0.17 (-0.25 to -0.084)‡ |
| TDI e', cm/s | -0.035 (-0.35 to 0.28) | 0.029 (-0.30 to 0.36) | -0.061 (-0.42 to 0.29) | 0.058 (-0.31 to 0.42) |
| E/e' | -0.048 (-0.73 to 0.63) | -1.06 (-1.75 to -0.36)† | 0.52 (-0.23 to 1.27) | -1.30 (-2.08 to -0.52) |
| LA volume index, mL/m$^2$ | -1.21 (-2.37 to -0.049)* | -1.08 (-2.25 to 0.082) | -0.90 (-2.22 to 0.43) | -0.65 (-1.98 to 0.68) |
| Ejection fraction, % | 0.033 (-0.64 to 0.70) | -0.72 (-1.38 to -0.054)* | 0.52 (-0.25 to 1.28) | -0.98 (-1.74 to -0.21)* |
| Longitudinal strain, % | 0.30 (-0.14 to 0.75) | -0.16 (-0.60 to 0.28) | 0.47 (-0.024 to 0.97) | -0.37 (-0.86 to 0.12) |
| Adjusted | | | | |
| Septal wall thickness, cm | 0.022 (0.004 to 0.040)* | 0.008 (-0.011 to 0.026) | 0.025 (0.004 to 0.046)* | -0.006 (-0.028 to 0.016) |
| Posterior wall thickness, cm | 0.013 (-0.004 to 0.030) | 0.002 (-0.016 to 0.019) | 0.017 (-0.003 to 0.036) | -0.008 (-0.028 to 0.013) |
| LV mass index, mg/m$^2$ | 2.82 (0.045 to 5.59)* | -0.019 (-2.95 to 2.92) | 3.93 (0.67 to 7.20)* | -2.22 (-5.66 to 1.22) |
| Relative wall thickness | 0.002 (-0.008 to 0.011) | 0.002 (-0.008 to 0.012) | 0.001 (-0.010 to 0.012) | 0.002 (-0.010 to 0.013) |
| E/A ratio | -0.067 (-0.14 to 0.010) | -0.15 (-0.23 to -0.073)‡ | 0.004 (-0.082 to 0.090) | -0.16 (-0.25 to -0.064)‡ |
| TDI e', cm/s | -0.034 (-0.36 to 0.30) | -0.032 (-0.38 to 0.32) | -0.025 (-0.40 to 0.35) | -0.019 (-0.42 to 0.39) |
| E/e' | -0.17 (-0.88 to 0.55) | -0.84 (-1.60 to -0.081)* | 0.28 (-0.53 to 1.10) | -0.99 (-1.86 to -0.12)* |
| LA volume index, mL/m$^2$ | -0.86 (-2.02 to 0.31) | 0.20 (-1.01 to 1.41) | -1.30 (-2.66 to 0.056) | 0.89 (-0.51 to 2.30) |
| Ejection fraction, % | -0.10 (-0.79 to 0.58) | -0.36 (-1.07 to 0.35) | 0.11 (-0.70 to 0.92) | -0.42 (-1.26 to 0.42) |
| Longitudinal strain, % | 0.21 (-0.25 to 0.67) | -0.10 (-0.56 to 0.36) | 0.34 (-0.19 to 0.86) | -0.26 (-0.79 to 0.27) |

Effect sizes (95% confidence interval) express the changes in the echocardiographic traits associated with a 1-SD increase in systolic (SBP) and diastolic (DBP) blood pressure. Adjusted estimates account for sex, age, ethnicity, body mass index, heart rate, current smoking, dyslipidemia, diabetes mellitus, use of antihypertensive medications by drug class i.e., diuretics, β-blocker, inhibitors of the renin-angiotensin, calcium-channel blockers, and intake of aspirin, lipid-lowering drugs, other cardiovascular medications, and antidiabetic agents. Longitudinal strain is a negative value, but for ease of interpretation longitudinal strain was expressed as an absolute value. Significance of the associations: * $P \leq 0.05$, † $P \leq 0.01$, and ‡ $P \leq 0.001$.

**Table S3. Cardiac Structure and Function in Relation to Blood Pressure in White.**

| Blood Pressure Model | Models Including a Single BP | | Models Including Two BP | |
|---|---|---|---|---|
| | SBP | DBP | SBP | DBP |
| Whites (n=770) | | | | |
| Septal wall thickness, cm | 0.013 (-0.001 to 0.027) | 0.006 (-0.009 to 0.021) | 0.015 (-0.002 to 0.031) | -0.003 (-0.021 to 0.015) |
| Posterior wall thickness, cm | 0.009 (-0.004 to 0.022) | 0.001 (-0.013 to 0.015) | 0.012 (-0.003 to 0.028) | -0.006 (-0.023 to 0.011) |
| LV mass index, mg/m$^2$ | 1.50 (-0.72 to 3.73) | 0.099 (-2.29 to 2.49) | 2.08 (-0.58 to 4.75) | -1.13 (-3.99 to 1.73) |
| Relative wall thickness | 0.002 (-0.005 to 0.009) | 0.002 (-0.006 to 0.010) | 0.001 (-0.007 to 0.010) | 0.001 (-0.008 to 0.010) |
| E/A ratio | -0.10 (-0.16 to -0.045)‡ | -0.17 (-0.24 to -0.11)‡ | -0.029 (-0.098 to 0.039) | -0.16 (-0.23 to -0.084)‡ |
| TDI e', cm/s | -0.12 (-0.36 to 0.13) | -0.15 (-0.42 to 0.12) | -0.065 (-0.35 to 0.22) | -0.11 (-0.43 to 0.21) |
| E/e' | -0.27 (-0.83 to 0.29) | -0.82 (-1.44 to -0.20)† | 0.16 (-0.49 to 0.81) | -0.92 (-1.64 to -0.19)* |
| LA volume index, mL/m$^2$ | -0.76 (-1.69 to 0.16) | -0.22 (-1.22 to 0.78) | -0.94 (-2.05 to 0.17) | 0.34 (-0.86 to 1.54) |
| Ejection fraction, % | -0.55 (-1.12 to 0.014) | -0.87 (-1.47 to -0.26)† | -0.15 (-0.83 to 0.53) | -0.78 (-1.50 to -0.055)* |
| Longitudinal strain, % | 0.22 (-0.15 to 0.58) | -0.16 (-0.54 to 0.22) | 0.40 (-0.025 to 0.82) | -0.37 (-0.81 to 0.072) |
| Non-Whites (n=165) | | | | |
| Septal wall thickness, cm | 0.045 (0.009 to 0.080)* | 0.034 (-0.004 to 0.072) | 0.039 (-0.004 to 0.082) | 0.011 (-0.035 to 0.056) |
| Posterior wall thickness, cm | 0.050 (0.018 to 0.082)† | 0.048 (0.013 to 0.082)† | 0.036 (-0.003 to 0.075) | 0.026 (-0.016 to 0.067) |
| LV mass index, mg/m$^2$ | 6.01 (1.36 to 10.7)* | 4.06 (-0.92 to 9.04) | 5.65 (-0.015 to 11.3) | 0.68 (-5.31 to 6.66) |
| Relative wall thickness | 0.018 (-0.001 to 0.037) | 0.023 (0.003 to 0.043)* | 0.009 (-0.015 to 0.032) | 0.018 (-0.007 to 0.042) |
| E/A ratio | 0.037 (-0.10 to 0.18) | -0.054 (-0.21 to 0.10) | 0.096 (-0.075 to 0.27) | -0.11 (-0.30 to 0.075) |
| TDI e', cm/s | -0.0002 (-0.56 to 0.56) | 0.29 (-0.31 to 0.89) | -0.23 (-0.91 to 0.45) | 0.44 (-0.30 to 1.18) |
| E/e' | -0.015 (-1.16 to 1.13) | -0.53 (-1.76 to 0.69) | 0.40 (-1.00 to 1.80) | -0.78 (-2.28 to 0.72) |
| LA volume index, mL/m$^2$ | 0.090 (-1.97 to 2.15) | 0.58 (-1.65 to 2.80) | -0.28 (-2.74 to 2.18) | 0.74 (-1.92 to 3.40) |
| Ejection fraction, % | 0.24 (-0.92 to 1.41) | 0.40 (-0.82 to 1.62) | 0.046 (-1.37 to 1.46) | 0.37 (-1.11 to 1.85) |
| Longitudinal strain, % | -0.39 (-1.18 to 0.39) | -0.74 (-1.57 to 0.091) | 0.020 (-0.94 to 0.98) | -0.75 (-1.80 to 0.29) |

Effect sizes (95% confidence interval) express the changes in the echocardiographic traits associated with a 1-SD increase in systolic (SBP) and diastolic (DBP) blood pressure. Adjusted estimates account for sex, age, body mass index, heart rate, current smoking, dyslipidemia, diabetes mellitus, use of antihypertensive medications by drug class i.e., diuretics, β-blockers, inhibitors of the renin-angiotensin, calcium-channel blockers, and intake of aspirin, lipid-lowering drugs, other cardiovascular medications, and antidiabetic agents. Longitudinal strain is a negative value, but for ease of interpretation longitudinal strain was expressed as an absolute value. Significance of the associations: * $P \leq 0.05$, † $P \leq 0.01$, and ‡ $P \leq 0.001$.

**Table S4. Cardiac Structure and Function in Relation to Blood Pressure by Median of Age.**

| Blood Pressure Model | Models Including a Single BP | | Models Including Two BP | |
|---|---|---|---|---|
| | SBP | DBP | SBP | DBP |
| Age <70 years | | | | |
| Septal wall thickness, cm | 0.036 (0.019 to 0.055)‡ | 0.019 (0.0001 to 0.038)* | 0.039 (0.017 to 0.061)‡ | -0.004 (-0.027 to 0.019) |
| Posterior wall thickness, cm | 0.036 (0.019 to 0.053)‡ | 0.019 (0.002 to 0.037)* | 0.037 (0.017 to 0.058)‡ | -0.003 (-0.024 to 0.018) |
| LV mass index, mg/m$^2$ | 5.70 (2.90 to 8.50)‡ | 3.00 (0.070 to 5.93) | 6.01 (2.59 to 9.43)‡ | -0.56 (-4.09 to 2.98) |
| Relative wall thickness | 0.010 (0.002 to 0.019)* | 0.007 (-0.002 to 0.016) | 0.009 (-0.001 to 0.020) | 0.002 (-0.009 to 0.013) |
| E/A ratio | -0.053 (-0.13 to 0.027) | -0.14 (-0.22 to -0.066)‡ | 0.036 (-0.057 to 0.13) | -0.16 (-0.26 to -0.070)‡ |
| TDI e', cm/s | -0.23 (-0.58 to 0.11) | -0.063 (-0.42 to 0.30) | -0.28 (-0.69 to 0.12) | 0.098 (-0.33 to 0.52) |
| E/e' | 0.39 (-0.28 to 1.06) | -0.67 (-1.36 to 0.017) | 1.03 (0.25 to 1.81)† | -1.24 (-2.05 to -0.44)† |
| LA volume index, mL/m$^2$ | -0.001 (-0.88 to 0.88) | -0.065 (-0.99 to 0.86) | 0.052 (-1.03 to 1.13) | -0.096 (-1.23 to 1.03) |
| Ejection fraction, % | -0.74 (-1.48 to 0.001) | -0.79 (-1.55 to -0.019)* | -0.45 (-1.36 to 0.45) | -0.52 (-1.45 to 0.42) |
| Longitudinal strain, % | -0.32 (-0.82 to 0.19) | -0.55 (-1.06 to -0.043)* | -0.024 (-0.62 to 0.58) | -0.54 (-1.14 to 0.071) |
| Age ≥70 years | | | | |
| Septal wall thickness, cm | 0.002 (-0.017 to 0.021) | 0.010 (-0.010 to 0.030) | -0.005 (-0.027 to 0.018) | 0.013 (-0.011 to 0.036) |
| Posterior wall thickness, cm | -0.001 (-0.019 to 0.017) | 0.009 (-0.010 to 0.027) | -0.008 (-0.029 to 0.013) | 0.013 (-0.009 to 0.035) |
| LV mass index, mg/m$^2$ | -0.96 (-3.84 to 1.92) | -0.34 (-3.34 to 2.66) | -1.09 (-4.50 to 2.32) | 0.26 (-3.29 to 3.81) |
| Relative wall thickness | -0.0001 (-0.010 to 0.010) | 0.009 (-0.002 to 0.019) | -0.006 (-0.019 to 0.006) | 0.012 (-0.001 to 0.025) |
| E/A ratio | -0.084 (-0.17 to -0.001)* | -0.14 (-0.23 to -0.050)† | -0.025 (-0.12 to 0.070) | -0.12 (-0.23 to -0.022)* |
| TDI e', cm/s | -0.018 (-0.32 to 0.29) | -0.048 (-0.38 to 0.28) | 0.007 (-0.36 to 0.37) | -0.052 (-0.44 to 0.34) |
| E/e' | -0.61 (-1.36 to 0.13) | -0.77 (-1.58 to 0.040) | -0.33 (-1.21 to 0.54) | -0.58 (-1.53 to 0.38) |
| LA volume index, mL/m$^2$ | -1.47 (-2.88 to -0.064)* | 0.047 (-1.44 to 1.53) | -2.07 (-3.73 to -0.42)* | 1.20 (-0.54 to 2.94) |
| Ejection fraction, % | -0.24 (-0.95 to 0.48) | -0.51 (-1.24 to 0.23) | 0.036 (-0.81 to 0.88) | -0.53 (-1.39 to 0.34) |
| Longitudinal strain, % | 0.37 (-0.074 to 0.82) | -0.12 (-0.59 to 0.35) | 0.58 (0.064 to 1.10)* | -0.43 (-0.97 to 0.11) |

Effect sizes (95% confidence interval) express the changes in the echocardiographic traits associated with a 1-SD increase in systolic (SBP) and diastolic (DBP) blood pressure. Adjusted estimates account for sex, age, ethnicity, body mass index, heart rate, current smoking, dyslipidemia, diabetes mellitus, use of antihypertensive medications by drug class i.e., diuretics, β-blocker, inhibitors of the renin-angiotensin, calcium-channel blockers, and intake of aspirin, lipid-lowering drugs, other cardiovascular medications, and antidiabetic agents. Longitudinal strain is a negative value, but for ease of interpretation longitudinal strain was expressed as an absolute value. Significance of the associations: * $P \leq 0.05$, † $P \leq 0.01$, and ‡ $P \leq 0.001$.