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QUARTERLY FOCUS ISSUE: HEART FAILURE

Contractility and Ventricular Systolic Stiffening in Hypertensive Heart Disease

Insights Into the Pathogenesis of Heart Failure With Preserved Ejection Fraction

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Objectives We sought to compare left ventricular (LV) systolic stiffness and contractility in normal subjects, hypertensive patients without heart failure, and patients with heart failure and preserved ejection fraction (HFpEF) and to determine whether LV systolic stiffness or myocardial contractility is associated with the rate of mortality in patients with HFpEF.

Background Arterial load is increased in patients with hypertension and is matched by increased end-systolic LV stiffness (ventricular-arterial coupling). Increased end-systolic LV stiffness may be mediated by enhanced myocardial contractility or processes that increase passive myocardial stiffness.

Methods Healthy control patients (n = 617), hypertensive patients (no heart failure, n = 719), and patients with HFpEF (n = 244, 96% hypertensive) underwent echo-Doppler characterization of arterial (Ea) and LV end-systolic (Ees) stiffness (elastance), ventricular-arterial coupling (Ea/Ees ratio), and chamber-level and myocardial contractility (stress-corrected midwall shortening).

Results We found that Ea and Ees were similarly increased in hypertensive patients with or without HFpEF compared with control patients, but ventricular-arterial coupling was similar across groups. In hypertensive patients, increased Ees was associated with enhanced chamber-level and myocardial contractility, whereas in patients with HFpEF, chamber and myocardial contractility were depressed compared with both hypertensive and control patients. Group differences persisted after adjusting for geometry. In patients with HFpEF, impaired myocardial contractility (but not Ees) was associated with increased age-adjusted mortality.

Conclusions Although arterial load is increased and matched by increased LV systolic stiffness in hypertensive patients with or without HFpEF, the mechanisms of systolic LV stiffening differ substantially. These data suggest that myocardial contractility increases to match arterial load in asymptomatic hypertensive heart disease, but that progression to HFpEF may be mediated by processes that simultaneously impair myocardial contractility and increase passive myocardial stiffness. (J Am Coll Cardiol 2009;54:410–8) © 2009 by the American College of Cardiology Foundation

One-half of patients with heart failure (HF) have a preserved ejection fraction (i.e., heart failure with preserved ejection fraction [HFpEF]) (1–4). Heart failure with preserved ejection fraction predominantly afflicts elderly, hypertensive patients (1,3,4). Vascular stiffness increases with age, promoting systolic hypertension and increased effective arterial elastance (Ea) (5,6). Left ventricular (LV) end-systolic stiffness (elastance) (Ees) increases in tandem (5–7), such that the relationship between ventricular and arterial elastance (ventricular-arterial coupling) remains relatively constant (8–10).

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End-systolic LV elastance is a measure of contractility, but it is also influenced by chamber geometry and passive myocardial stiffening (8,11). Ees is increased in patients with HFpEF (7,10), yet many studies (12–14), though not all (15), have reported that various systolic function indices are mildly depressed in patients with HFpEF. Indeed, it is well recognized that impairments in myocardial contractility may coexist with preserved ejection fraction (EF) in hypertensive patients with

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concentric remodeling (16–20). This phenomenon allows the preservation of endocardial motion despite reduced shortening of individual myofibers, such that the EF remains normal (19,21).

We sought to compare and contrast chamber and myocardial contractility, LV Ees, and ventricular-arterial coupling in 3 groups, healthy control patients without cardiovascular disease, hypertensive patients without HF, and patients with HFpEF, by using multiple load-independent measures of chamber and myocardial contractility. All participants were drawn from a large-scale, nonselected, population-based sample. To account for differences in ventricular geometry, contractile indices were contrasted within each pattern of chronic chamber remodeling. To determine the clinical significance of these findings, the relationships between contractility or LV systolic stiffness and mortality were examined.

Methods

Study population and setting. The unique aspects of the Rochester Epidemiology Project for population-based research have been described (2,3). The study was approved by the Mayo Institutional Review Board. A random sample (n = 2,042) of the Olmsted County, Minnesota, population age ≥45 years underwent echocardiography and record review. From this cohort, 2 control groups were identified (2,3,10): healthy, nonobese control patients without cardiovascular disease or diabetes, and hypertensive control patients without HF. From the same community, consecutive patients with HFpEF and no significant valvular disease were identified by use of the Framingham criteria (2,3). Vital status through March 2008 was determined from the Mayo Clinic registration database and the Rochester Epidemiology Project death database (2,3). Mortality data were ascertained from medical records, death certificates for Olmsted County residents, obituaries, and notices of death in the local newspapers. Data on all Minnesota deaths were obtained from the State of Minnesota annually. Some clinical characteristics and ventricular function parameters from subjects in this study have previously been published (1–3,10), but most of the systolic indices and their associations with outcomes have not.

Echocardiography. Comprehensive echocardiographic assessment was performed by registered diagnostic cardiac sonographers by the use of standardized instruments and techniques, with studies interpreted in a blinded fashion (10). Ventricular dimensions, wall thickness, chamber volumes, and stroke volume were determined in triplicate from 2-dimensional, M-mode echocardiography, and Doppler spectra with the use of standard methods (10). Sex-specific definitions for ventricular hypertrophy and geometry patterns based on LV mass index and relative wall thickness (normal, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy) were used (10). Left ventricular end-diastolic pressure was estimated from echo-Doppler and tissue-Doppler (10). Brachial blood pressure was determined by sphygmomanometry. End-systolic pressure was determined from the product of: 0.9 × systolic blood pressure (8). Effective arterial elastance (Ea = end-systolic pressure/stroke volume) and circumferential end-systolic wall stress (cESS) were determined as measures of ventricular afterload (8,19).

Abbreviations and Acronyms

- **cESS** = circumferential end-systolic stress
- **Ea** = effective arterial elastance (stiffness)
- **Ees** = end-systolic elastance (stiffness)
- **EF** = ejection fraction
- **HF** = heart failure
- **HFpEF** = heart failure with preserved ejection fraction
- **LV** = left ventricle
- **PRSW** = pre-load recruitable stroke work
- **sc-eFS** = stress-corrected endocardial fractional shortening
- **sc-mFS** = stress-corrected midwall fractional shortening

Assessment of LV systolic chamber and arterial properties. Endocardial fractional shortening (eFS) was determined from 2-dimensional systolic and diastolic dimensions. Left ventricular Ees was determined by the single-beat technique (22). Ventricular-arterial interaction was quantified by the coupling ratio (Ea/Ees). To account for both afterload and pre-load, 2 additional load-independent measures of chamber contractility were examined: 1) wall-stress-corrected endocardial fractional shortening (sc-eFS), which was determined by expressing observed eFS as a percentage of that predicted for any given wall stress, based upon the regression equation derived in the healthy control patients (18); and 2) pre-load recruitable stroke work (PRSW), which was determined by the use of a validated single-beat technique (23).

Assessment of myocardial contractility. Measures of chamber-level contractility do not necessarily reflect myocardial contractility (16–19,21) because motion at the endocardial surface is greater than predicted by sarcomere shortening alone as the result of the phenomenon of cross-fiber shortening. Shortening of muscle fibers oriented in orthogonal directions at the inner and outer surfaces of the heart causes marked thickening in the radial axis (21). This effect is enhanced in the setting of concentric remodeling, allowing individual reductions in myofiber contraction to achieve the same net displacement of endocardium, preserving endocardial-based parameters such as EF (16,18,19,21). To assess myocardial contractility, circumferential midwall fractional shortening (mFS) was assessed by use of the 2-shell method of Shimizu and others (16–19). To minimize afterload dependence, stress-corrected midwall fractional shortening (sc-mFS) was determined as a percentage of that predicted for any given wall stress using the regression equation derived from the healthy control population (18).

Statistical methods. Categorical variables were compared by the chi-square test, and continuous variables were compared by the use of 1-way analysis of variance with Bonferroni correction. Regression analysis was used to adjust for age, sex, body size, chamber size and morphology, or the presence of other diseases, where the dependent variable was

Table 1 Subject Characteristics

	Control Patients (n = 617)	Hypertensive Patients (n = 719)	HFpEF Patients (n = 244)
Demographics			
Age (yrs)	57 (45–96)	66 (46–91)*	76 (22–99) *†
Female (%)	55	56	55
Body mass index (kg/m^2)	25.4 ± 2.7	29.8 ± 5.9*	32.2 ± 20.7*†
Hypertension (%)	0	100*	96*
Coronary artery disease (%)	0	16*	53*†
Diabetes mellitus (%)	0	11*	37*†
Estimated glomerular filtration rate (ml/min/1.73 m^2)	74.4 ± 14.1	74.7 ± 37.0	64.3 ± 28.1*†
Chronic beta-blocker use (%)	2	29*	74*†
Hemodynamics and LV morphology			
Systolic BP (mm Hg)	118 ± 12	143 ± 21*	132 ± 23*†
Diastolic BP (mm Hg)	70 ± 8	76 ± 11*	67 ± 14†
LV mass index (g/m^2)	88.8 ± 16.3	100.2 ± 22.7*	102.1 ± 29.0*
Relative wall thickness	0.38 ± 0.06	0.42 ± 0.07*	0.45 ± 0.10*†
Percent with LV hypertrophy (%)	18	40*	42*

*$p < 0.05$ versus control patients. †$p < 0.05$ versus hypertensive patients.
BP = blood pressure; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular.

the normally distributed continuous (linear least-squares regression) or categorical (logistic regression) outcome variable of interest. Any interaction between these variables also was evaluated and accounted for as appropriate. The Kaplan-Meier method tested for differences in survival between groups by the log-rank test. Cox proportional-hazards regression was used to adjust for the effect of differences in baseline characteristics on survival.

Results

Subject characteristics. Of 2,042 randomly selected community residents, 617 met the criteria for the healthy control group, and 719 subjects met the criteria for the hypertension without HF group. A total of 244 patients constituted the HFpEF group. Nearly all patients with HFpEF had a history of hypertension and were older, more obese, and had a greater prevalence of coronary artery disease and diabetes than hypertensive or control patients (Table 1).

Ventricular-arterial stiffness and coupling. Hypertensive patients and patients with HFpEF displayed increased afterload (Ea and cESS) compared with control patients (Table 2). Although Ea was similarly increased in hypertensive patients and patients with HFpEF, cESS was greater in patients with HFpEF. As previously reported in this population (10), Ees was similarly increased in hypertensive and HFpEF patients compared with control patients (Table 2). Overall, Ees was strongly correlated with Ea (Fig. 1A), and both this relationship and the mean

Table 2 Load, Contractility, and Ventricular-Arterial Coupling

	Control Patients (n = 617)	Hypertensive Patients (n = 719)	HFpEF Patients (n = 244)
LV afterload			
cESS (kdyne/cm^2)	90.8 ± 21	98.9 ± 28.5*	105.5 ± 35.4*†
Ea (mm Hg/ml)	1.30 ± 0.30	1.50 ± 0.41*	1.53 ± 0.43*
Ventricular arterial coupling			
Ees (mm Hg/ml)	1.99 ± 0.59	2.30 ± 0.80*	2.42 ± 0.90*
Ea/Ees	0.68 ± 0.13	0.68 ± 0.17	0.69 ± 0.22
Systolic function (%)			
EF	63 ± 5	65 ± 6	62 ± 6*†
eFS	39.7 ± 5.1	41.3 ± 5.7*	35.9 ± 6.6*†
mFS	20.9 ± 2.5	21.5 ± 2.7‡	18.5 ± 3.0*†
Load-independent measures of contractility			
PRSW (g/cm^2)	84.5 ± 18.6	99.3 ± 25.5*	78.7 ± 31.1*†
sc-eFS (% of predicted)	100 ± 8	108 ± 11*	96 ± 12*†
sc-mFS (% of predicted)	100 ± 10	105 ± 12*	91 ± 13*†

*$p < 0.005$ versus control patients. †$p < 0.0001$ versus hypertensive patients (unadjusted).
cESS = circumferential end-systolic stress; Ea = effective arterial elastance; Ees = end-systolic elastance; EF = ejection fraction; eFS = endocardial fractional shortening; mFS = midwall fractional shortening; PRSW = pre-load recruitable stroke work; sc = stress-corrected; other abbreviations as in Table 1.

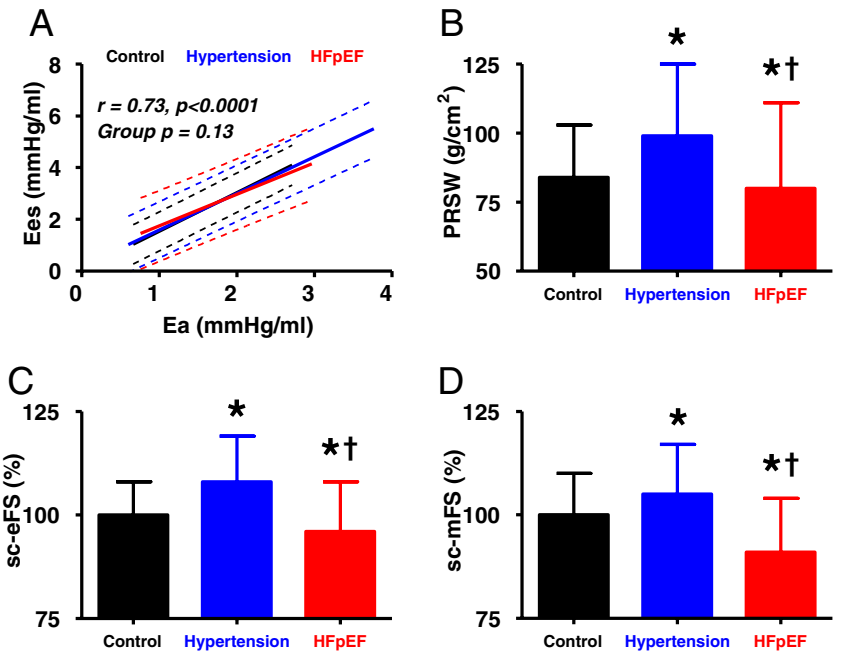

Figure 1 VA Coupling and Contractility

(A) The relationship between Ees and Ea was similar among each group (**dashed lines** show 95% prediction bands). **(B to D)** Load-independent chamber contractility (PRSW and sc-eFS) and myocardial contractility (sc-mFS) were increased in hypertensive patients without HF and decreased in patients with HFpEF compared with hypertensive and control patients. Data are mean ± SD. *p < 0.05 versus control; †p < 0.05 versus hypertension. Ea = effective arterial elastance; Ees = end-systolic elastance; eFS = endocardial fractional shortening; HFpEF = heart failure with preserved ejection fraction; mFS = midwall fractional shortening; PRSW = pre-load recruitable stroke work; sc = stress-corrected; VA = ventricular-arterial.

coupling ratios (Ea/Ees) were similar in all 3 groups (Table 2), indicating preserved ventricular-arterial coupling.

Left ventricular chamber and myocardial systolic properties. As compared with control patients, EF was similar but eFS and mFS were greater in the hypertensive group. In contrast, in patients with HFpEF, EF, eFS, and mFS were reduced as compared with hypertensive or control patients (Table 2). Similarly, load-independent measures of chamber contractility (PRSW and sc-eFS) were greater in hypertensive patients as compared with control patients and lower in HFpEF compared with hypertensive or control patients (Table 2, Fig. 1). Adjusting for wall stress (cESS), mFS was greater in hypertensive patients compared with control patients (Fig. 2A) and lower in patients with HFpEF compared with control patients (Fig. 2B) and hypertensive patients (Fig. 2C). Patients with HFpEF displayed lower sc-mFS than hypertensive or control patients (Table 2, Fig. 1), even after adjusting for age, sex, body size, renal function, beta-blocker use, history of coronary disease, and diabetes ($p < 0.0001$). The cumulative distribution of sc-mFS was shifted rightward from control patients in hypertension and leftward in HFpEF (Fig. 2D), indicating that myocardial contractility was systematically enhanced in hypertensive and impaired in HFpEF patients.

Relationships of geometry to contractility. As previously described in this cohort (3,10), relative wall thickness increased from control patients to hypertension to HFpEF (Table 1). The prevalence of LV hypertrophy was similarly increased in hypertensive and HFpEF patients. The distribution of geometry among hypertensives and HFpEF patients was different from that of control patients (Fig. 3A) and tended to be different in HFpEF versus hypertensive patients ($p = 0.045$).

In healthy control patients, Ees (Fig. 3B) and most contractile indices (Fig. 3C) were systematically elevated or reduced as a function of chamber geometry alone. To adjust for confounding effects of chamber remodeling between the groups, we compared Ees and each contractile index within each geometry pattern. Figure 4 shows that, regardless of geometry, Ees was consistently increased in hypertensive patients and patients with HFpEF as compared with control patients, whereas PRSW, sc-eFS, and sc-mFS were each consistently greater in hypertensive patients as compared with control patients and lower in HFpEF as compared with both hypertensive and control patients.

Myocardial contractility and outcomes. Median follow-up was 3.1 years (mean 3.1 ± 0.6 years) in the HFpEF group. Mortality at 3 years was 36.4% in patients with HFpEF, 3.1% in patients with hypertension, and 0.8% in control patients. In the HFpEF group, survival decreased with greater impairment of myocardial contractility (Fig. 5). After adjusting for age, sc-mFS below the median was

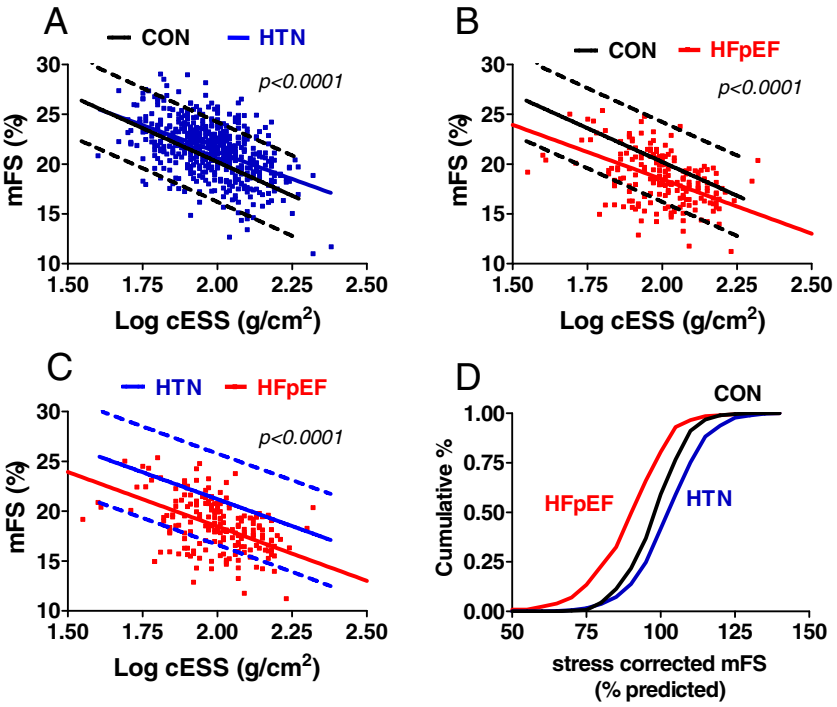

Figure 2 **Myocardial Contractility**

(A) The relationship between midwall myofiber shortening (mFS) and end-systolic wall stress (log cESS) showing mean regression **(solid line)** and 95% confidence limits **(dotted line)** in control patients (CON; **black line**) with data points and regression line for hypertensive patients (HTN; **blue line**) shifted upward, indicating enhanced myocardial contractility in hypertension. **(B to C)** In patients with HFpEF **(red lines)**, the data points and regression line are shifted down as compared with both control **(black line)** and hypertensive **(blue line)** patients, indicating depressed contractility. **(D)** Cumulative distribution plot for sc-mFS show that compared with healthy control patients (CON; **black line**), myocardial contractility is depressed in HFpEF **(red line)** and enhanced in hypertensive patients without HF (HTN; **blue line**). Abbreviations as in Figure 1.

associated with a 33% increase in mortality ($p = 0.013$). Impaired sc-mFS remained a significant predictor of mortality after adjusting for age, body mass index, coronary disease, hypertension, and diabetes mellitus ($p = 0.01$). In contrast, EF, Ees, Ea, and geometry pattern were not associated with age-adjusted mortality ($p > 0.05$).

Discussion

This is the largest population-based study to date examining LV systolic properties in patients with HFpEF, exploring the mechanisms underlying ventricular-arterial coupling in hypertensive heart disease according to the presence or absence of HFpEF. Among hypertensive patients, increases in end-systolic LV stiffness were associated with increased chamber and myocardial contractility. In contrast, similar increases in HFpEF patients were associated with impaired contractility, suggesting that increased Ees may be related to passive myocardial stiffening to a greater extent in this group. Disparities in contractile function were not due to differences in chamber geometry, and impaired myocardial contractility in HFpEF was associated with increased rates of mortality. We speculate that, over time, patients with hypertensive heart disease who develop HFpEF acquire structural or functional perturbations that impair myocardial contractility, and that these perturbations contribute to the transition to and progression of overt HF, despite preserved EF.

Ventricular-arterial coupling. The interaction of the heart with the arterial system (ventricular-arterial coupling) is a key determinant of cardiovascular performance (8,9). Ea is a lumped parameter reflecting total arterial afterload, incorporating mean and pulsatile components. Ees is determined invasively from the slope and intercept of the end-systolic pressure/volume relationship but may also be measured noninvasively (22), allowing Ees to be determined in larger patient populations. Ventricular-arterial coupling is expressed by the Ea/Ees ratio (8).

Although EF is the most commonly used measure of systolic function in clinical practice, it is potently influenced by loading conditions and chamber remodeling (24,25). Ejection fraction is more accurately conceptualized as a measure of ventricular-arterial coupling. Under normal circumstances, the Ea/Ees ratio varies from 0.5 to 1.0, a range in which cardiac work and efficiency are optimized (8,9). Although normal ventricular-arterial coupling ratios (and EF) were observed in each patient group, there were dramatic differences in the ways in which coupling was

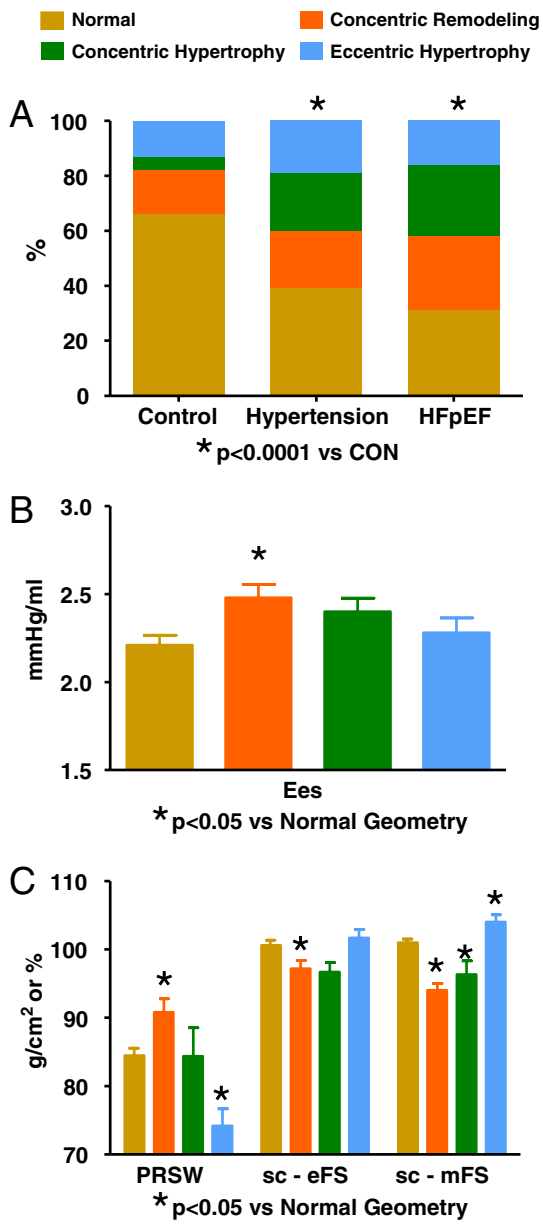

Figure 3 Geometry and Its Effect on End-Systolic Elastance and Contractility Indexes

(A) The distributions of LV geometry differed among control, hypertensive, and HFpEF patients. Even within the healthy control group, Ees varied according to geometry pattern **(B)**, as did PRSW, sc-eFS, and sc-mFS **(C)**. See text for discussion. Data are mean ± standard error. LV = left ventricular; other abbreviations as in Figures 1 and 2.

maintained—enhanced contractility in hypertensive patients without HF but impaired contractility in patients with HFpEF.

It is well recognized that changes in contractile performance alter Ees (22,24), but Ees is also influenced by chamber geometry and by factors that alter the passive stiffness of the myocardium (8,11). With aging, increases in arterial stiffness are associated with tandem increases in both systolic and diastolic LV stiffness (5,6,8). Indeed, in this study population, we have previously reported that diastolic ventricular stiffness is increased in both hypertensive and HFpEF patients compared with healthy control patients but is greatest in patients with HFpEF (10). Taken together with the current findings of impaired contractility despite increased Ees in patients with HFpEF, we speculate that the processes that contribute to diastolic stiffening in HFpEF influence systolic stiffness as well.

Contractility and coupling in patients with HFpEF. Seminal reports from the 1980s and 1990s (16–19,21) demonstrated that abnormal myocardial contractility may coexist with a normal EF because concentric geometric chamber remodeling preserves the extent of endocardial motion relative to the diastolic cavity. A number of studies (12,26–29) have reported abnormalities in regional systolic function in patients with HFpEF, particularly shortening in the longitudinal axis. However, the significance of these findings has been questioned (30) because systolic velocities vary inversely with afterload (31), typically increased in HFpEF patients (8,10), and because longitudinal shortening does not fully reflect chamber-level contractility (30). By examining load-independent parameters of chamber and myocardial contractility in a large, population-based study, we show that patients with HFpEF indeed do display systolic dysfunction compared with both hypertensive patients without HF and healthy control patients.

The authors of 2 important but smaller-sized studies (14,15) also found that roughly one-third of patients with HFpEF were below the 95% prediction bands for the relationship between mFS and cESS observed in healthy control patients. More important, >90% of patients with HFpEF fell below the mean regression line describing healthy control patients. This finding is consistent with the systematic shift in the distribution of myocardial contractility in HFpEF observed in the current study. However, previous studies did not compare HFpEF with hypertensive control patients, HFpEF subjects were highly selected, there were no adjustments for differences in LV geometry, and the impact of impaired myocardial contractility on survival was not examined (12,15,26–28).

Ees increases with decreasing LV size, yet even after adjusting for differences in geometry, Ees remained significantly increased in patients HFpEF, whereas each additional load-independent index of chamber-level and myocardial contractility was impaired. This "disconnect" between Ees and other measures of contractility has been observed in animal models of pressure overload HF, where increased Ees coexists with impaired chamber, myocardial, and myocyte contractility; fibrosis; diastolic dysfunction; and impaired beta-adrenergic signaling (32). The association of resting contractile dysfunction with increased mortality in patients with HFpEF, viewed in light of these animal studies and recent studies demonstrating abnormal contractile reserve with stress in HFpEF (33–35), indicates that impaired contractility, however mild at rest,

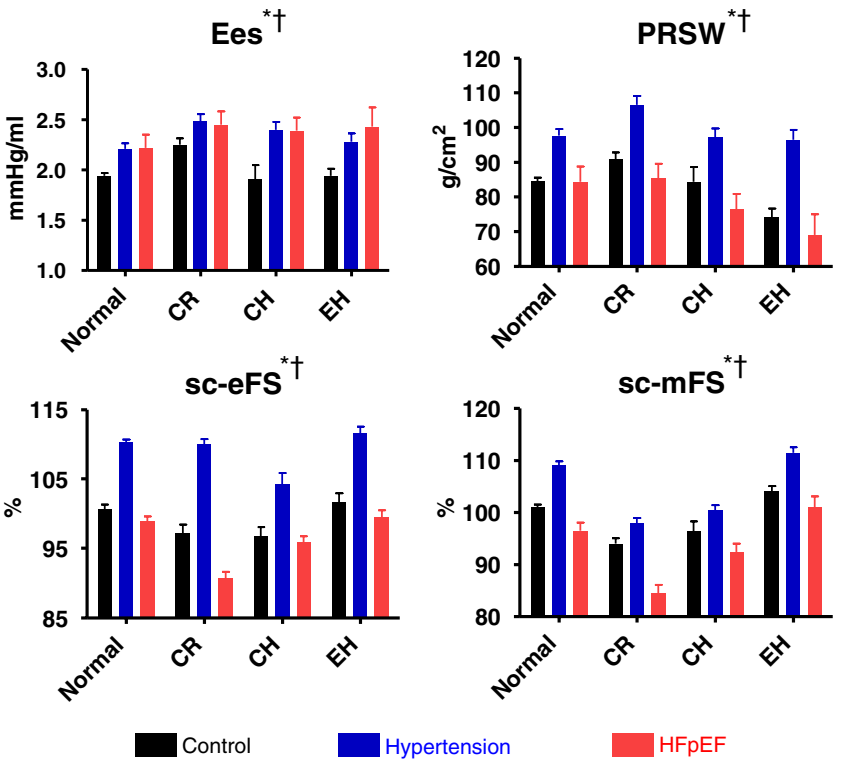

Figure 4 VA Coupling and Contractility According to Group and Geometry

(A) Ees was elevated in HFpEF **(red)** and hypertensive patients **(blue)** compared with control patients **(black)** for each pattern of geometry. In contrast, PRSW **(B)**, sc-eFS **(C)**, and sc-mFS **(D)** were each consistently depressed in HFpEF and increased in hypertensive patients compared with control patients. See text for discussion. Data are mean ± standard error. *Geometry $p < 0.0001$; †group $p < 0.0001$. CH = concentric hypertrophy; CR = concentric remodeling; EH = eccentric hypertrophy; other abbreviations as in Figure 1.

may not simply be an innocuous bystander in HFpEF but rather may reflect processes that mediate progression to overt HF.

Contractility and coupling in hypertension without HF. Hypertension is a dominant risk factor for patients with HFpEF (1,4), and many of the cardiovascular features in HFpEF are also found in asymptomatic hypertensive patients (13,33). As such, comparisons between these 2 groups provide valuable mechanistic insight into what specifically distinguishes the HFpEF phenotype. Although increased Ees in patients with HFpEF coexisted with impaired contractility, increased Ees was associated with enhanced contractility in hypertensives. Earlier studies have reported reduced myocardial contractility in hypertension, and that the presence of impaired myocardial contractility is associated with greater rates of cardiovascular events (13,16,18,19,36). However, the patient groups populating these earlier referral-based studies were often pre-selected for the presence of hypertrophy and had more extreme levels of concentric remodeling (13,16,18,19). We also found that sc-mFS was categorically impaired in the presence of concentric relative to normal geometry—regardless of patient group (Figs. 3 and 4).

However, within each geometry pattern, contractility was consistently enhanced in hypertensive patients without HF. The hypertensive patients in the current study were younger than the patients with HFpEF, and it may be that most of the hypertensive control patients in this population-based study were at an "earlier" stage of disease, where enhanced contractility may be observed as has been reported in human (37,38) and animal studies (39).

Alternatively, hypertensives in this more contemporary, population-based study may have been more optimally treated (40) because the extent of concentric remodeling was not as extreme as witnessed in earlier referral-based studies. If hypertensive heart disease and HFpEF exist in a continuum as has been suggested (10), it may be that the processes leading to concomitant loss of contractile hyperfunction and passive stiffening play a role in the transition from hypertension to clinically evident HFpEF. Alternatively, the myocardial response to pressure overload may differ in patients predisposed to develop HFpEF. These concepts merit future study in chronic longitudinal studies.

Study limitations. The methods used to assess systolic function are validated against gold standard techniques (10,22,23), but echo-Doppler data inherently have greater

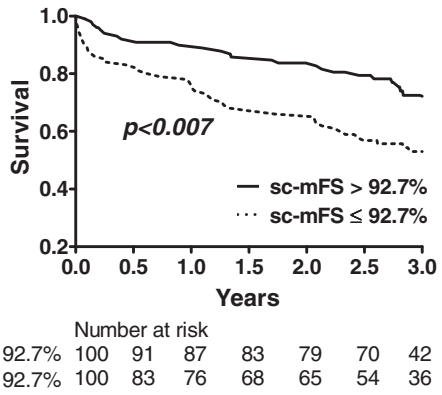

Figure 5 **Kaplan-Meier Plot of Survival in Patients With HFpEF**

Stress-corrected midwall myofiber shortening (sc-mFS) below the median value is associated with reduced survival in patients with HFpEF. Abbreviations as in Figure 1.

variability compared with invasive measurements. Although sampling bias was minimal in this population-based study, our study cohort comprised almost exclusively white patients, and these results may not be applicable to other ethnic groups. Cause-of-death data are not available from this population, and we are unable to determine how impaired contractility might be related to mode of death. These data are observational in nature and therefore cannot prove causality or temporal progression.

Conclusions

Although EF and ventricular-arterial coupling are similarly "normal" in hypertensive patients with or without HFpEF, the mechanisms whereby LV systolic elastance increase to match arterial load differs according to the presence of HF. Patients with hypertension without HF display enhanced Ees and contractility, whereas the Ees in patients with HFpEF is increased despite impaired contractility at both the chamber and myocardial levels. These differences are independent of geometry, and myocardial contractile dysfunction is associated with increased mortality in HFpEF, emphasizing its clinical importance. Therapies targeting processes that mediate concomitant contractile dysfunction and passive stiffening may prove useful in the treatment of patients with HFpEF.

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REFERENCES

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.
2. Redfield MM, Jacobsen SJ, Burnett JC Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.
3. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. JAMA 2006;296:2209–16.
4. Klapholz M, Maurer M, Lowe AM, et al. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. J Am Coll Cardiol 2004;43:1432–8.
5. Chen CH, Nakayama M, Nevo E, Fetics BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: implications for pressure regulation and cardiac reserve in the elderly. J Am Coll Cardiol 1998;32:1221–7.
6. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation 2005;112:2254–62.
7. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003;107:714–20.
8. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. Heart Fail Clin 2008;4:23–36.
9. Chantler PD, Lakatta EG, Najjar SS. Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise. J Appl Physiol 2008;105:1342–51.
10. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007;115:1982–90.
11. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol 2005;289:H501–12.
12. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. Circulation 2002;105:1195–201.
13. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. J Am Coll Cardiol 2007;49:198–207.
14. Vinch CS, Aurigemma GP, Simon HU, Hill JC, Tighe DA, Meyer TE. Analysis of left ventricular systolic function using midwall mechanics in patients >60 years of age with hypertensive heart disease and heart failure. Am J Cardiol 2005;96:1299–303.
15. Baicu CF, Zile MR, Aurigemma GP, Gaasch WH. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. Circulation 2005;111:2306–12.
16. Shimizu G, Hirota Y, Kita Y, Kawamura K, Saito T, Gaasch WH. Left ventricular midwall mechanics in systemic arterial hypertension. Myocardial function is depressed in pressure-overload hypertrophy. Circulation 1991;83:1676–84.
17. Shimizu G, Zile MR, Blaustein AS, Gaasch WH. Left ventricular chamber filling and midwall fiber lengthening in patients with left ventricular hypertrophy: overestimation of fiber velocities by conventional midwall measurements. Circulation 1985;71:266–72.
18. de Simone G, Devereux RB, Roman MJ, et al. Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension. J Am Coll Cardiol 1994;23:1444–51.
19. Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 1995;26:195–202.
20. Rosen BD, Edvardsen T, Lai S, et al. Left ventricular concentric remodeling is associated with decreased global and regional systolic function: the Multi-Ethnic Study of Atherosclerosis. Circulation 2005;112:984–91.
21. de Simone G, Devereux RB. Rationale of echocardiographic assessment of left ventricular wall stress and midwall mechanics in hypertensive heart disease. Eur J Echocardiogr 2002;3:192–8.

22. Chen CH, Fetics B, Nevo E, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001;38:2028–34.
23. Lee WS, Huang WP, Yu WC, Chiou KR, Ding PY, Chen CH. Estimation of preload recruitable stroke work relationship by a single-beat technique in humans. Am J Physiol Heart Circ Physiol 2003;284:H744–50.
24. Kass DA, Maughan WL, Guo ZM, Kono A, Sunagawa K, Sagawa K. Comparative influence of load versus inotropic states on indexes of ventricular contractility: experimental and theoretical analysis based on pressure-volume relationships. Circulation 1987;76:1422–36.
25. Konstam MA. "Systolic and diastolic dysfunction" in heart failure? Time for a new paradigm. J Card Fail 2003;9:1–3.
26. Petrie MC, Caruana L, Berry C, McMurray JJ. "Diastolic heart failure" or heart failure caused by subtle left ventricular systolic dysfunction? Heart 2002;87:29–31.
27. Yip G, Wang M, Zhang Y, Fung JW, Ho PY, Sanderson JE. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? Heart 2002;87:121–5.
28. Brucks S, Little WC, Chao T, et al. Contribution of left ventricular diastolic dysfunction to heart failure regardless of ejection fraction. Am J Cardiol 2005;95:603–6.
29. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J 2008;29:1283–9.
30. Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. Circulation 2006;113:296–304.
31. Borlaug BA, Melenovsky V, Redfield MM, et al. Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. J Am Coll Cardiol 2007;50:1570–7.
32. Perrino C, Naga Prasad SV, Mao L, et al. Intermittent pressure overload triggers hypertrophy-independent cardiac dysfunction and vascular rarefaction. J Clin Invest 2006;116:1547–60.
33. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 2006;114:2138–47.
34. Ennezat PV, Lefetz Y, Marechaux S, et al. Left ventricular abnormal response during dynamic exercise in patients with heart failure and preserved left ventricular ejection fraction at rest. J Card Fail 2008;14:475–80.
35. Borlaug BA, Lam CSP, Olson TP, Flood KS, Johnson BD, Redfield MM. Cardiovascular reserve function in heart failure with preserved ejection fraction: systolic versus diastolic determinants (abstr). Circulation 2008;118:S1022.
36. de Simone G, Devereux RB, Koren MJ, Mensah GA, Casale PN, Laragh JH. Midwall left ventricular mechanics. An independent predictor of cardiovascular risk in arterial hypertension. Circulation 1996;93:259–65.
37. Hartford M, Wikstrand JC, Wallentin I, Ljungman SM, Berglund GL. Left ventricular wall stress and systolic function in untreated primary hypertension. Hypertension 1985;7:97–104.
38. Palatini P, Bongiovi S, Mario L, Schiraldi C, Mos L, Pessina AC. Above-normal left ventricular systolic performance during exercise in young subjects with mild hypertension. Eur Heart J 1995;16:232–42.
39. Jegger D, da Silva R, Jeanrenaud X, et al. Ventricular-arterial coupling in a rat model of reduced arterial compliance provoked by hypervitaminosis D and nicotine. Am J Physiol Heart Circ Physiol 2006;291:H1942–51.
40. Perlini S, Muiesan ML, Cuspidi C, et al. Midwall mechanics are improved after regression of hypertensive left ventricular hypertrophy and normalization of chamber geometry. Circulation 2001;103:678–83.

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