

## Women Have Higher Left Ventricular Ejection Fractions Than Men Independent of Differences in Left Ventricular Volume The Dallas Heart Study

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**Background**—Although gender-specific criteria are common for defining cardiac traits such as left ventricular hypertrophy, left ventricular ejection fraction (LVEF) thresholds widely used in clinical practice have traditionally been the same for women and men, perhaps because it remains uncertain whether there is a systematic difference in LVEF between genders.

**Methods and Results**—Using cardiac magnetic resonance imaging in a probability-based sample of Dallas County residents aged 30 to 65 years (1435 women and 1183 men), we compared LVEF in women and men. The association of gender with stroke volume independent of end-diastolic volume (EDV) or other potential confounders was assessed by multivariable analysis. Gender-specific thresholds for a low LVEF were defined at the 2.5th percentile in women and men from a healthy reference subpopulation. The median (25th, 75th percentile) LVEF was higher in women than in men (75% [70%, 79%] in women versus 70% [65%, 75%] in men,  $P < 0.001$ ). Left ventricular EDV and end-systolic volume indexed to body surface area were smaller in women than in men ( $P < 0.001$  for both). Gender remained significantly associated with stroke volume, independent of EDV and other potential confounders in multivariable analysis. A low LVEF was defined as below 61% in women and below 55% in men.

**Conclusions**—Women have a higher LVEF than men in the general population, secondary to a higher stroke volume for a given EDV independent of known potential confounders. (*Circulation*. 2006;113:1597-1604.)

**Key Words:** cardiac volume ■ epidemiology ■ heart failure ■ magnetic resonance imaging  
■ myocardial contraction

Although left ventricular ejection fraction (LVEF) is a load-sensitive measure of systolic function, it is routinely used in making clinical decisions, such as when to insert an automatic implantable cardiac defibrillator or whether to classify a patient as having systolic heart failure (low LVEF) or diastolic heart failure (preserved LVEF), a critical branch point in many treatment algorithms.<sup>1</sup> Although gender-specific criteria are common for other cardiac traits, such as left ventricular hypertrophy,<sup>2</sup> to date, the threshold LVEF in clinical decision-making has been the same for men and women, perhaps because it remains unclear whether LVEF differs between genders. Some echocardiographic studies show higher LVEF in women than in men,<sup>3-6</sup> but some magnetic resonance imaging (MRI) studies have found comparable LVEFs between genders.<sup>7-9</sup> Furthermore, even if there are gender differences in LVEF, it remains entirely unclear whether the smaller ventricular volumes that are present in women explain this difference, possibly because previous large population-based studies used 2-dimensional

echocardiography, which has limitations in accurately measuring ventricular volume.<sup>10</sup>

### Clinical Perspective p 1604

To further elucidate this issue, we examined the following 2 hypotheses: (1) LVEF as measured by cardiac MRI will systematically differ between women and men in the general population, and (2) this gender difference will be independent of potential confounders, including differences in left ventricular volume.

### Methods

#### Study Population

The Dallas Heart Study (DHS) is a multiethnic probability-based sample of Dallas County residents aged 18 to 65 years; data were collected over 3 visits.<sup>11</sup> The first visit was at the participant's home and included a health survey administered to 6101 civilian noninstitutionalized residents. At the second home visit, blood and urine specimens were obtained from 3398 adults aged 30 to 65 years. At the third visit, 2971 participants aged 30 to 67 years underwent

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sophisticated imaging tests, including cardiac MRI and dual energy x-ray absorptiometry (DEXA) at the University of Texas Southwestern Medical Center, Dallas. Black patients were intentionally oversampled so that the final sample included an equal number of black and non-black subjects. Informed consent was obtained for all participants, and the study protocol was approved by the institutional review board.

In the present study, we included subjects who completed all 3 visits of the DHS and had a measurable LVEF ( $n=2705$ ). From those, we excluded participants who self-reported valvular abnormalities ( $n=81$ ), congenital heart defects ( $n=4$ ), or both ( $n=2$ ), leaving a final study sample of 2618.

### Cardiac MRI

MRI was performed by using 2 comparable 1.5-T MRI systems (Philips Medical Systems, Best, the Netherlands) as previously described.<sup>2</sup> Briefly, short-axis breath-hold electrocardiographic-gated cine magnetic resonance images were obtained from the apex to the base of the left ventricle with use of the following parameters: slice, 6 mm; gap, 4 mm; field of view, 36 to 40 cm; acquired pixel size at 36-cm field of view,  $1.29 \times 2.58$ ; and temporal resolution, 40 ms. A turbo field echo sequence (TFE) was used in 93.5% of the cohort. A steady-state free precession sequence (SSFP) was used in the remaining 6.5%, and these values were adjusted by using regression equations derived from a subset of subjects ( $n=60$ ) who had both sequences performed. Thus, all values are reported for a TFE sequence to permit comparison with prior studies. The regression equations were as follows:  $EDV_{TFE}$  (mL) =  $0.8020 \times EDV_{SSFP} + 11.904$ ;  $ESV_{TFE}$  (mL) =  $0.8172 \times ESV_{SSFP} - 1.0188$ ;  $LVM_{TFE}$  (g) =  $0.9588 \times LVM_{SSFP} + 17.53$ , where EDV is end-diastolic volume, ESV is end-systolic volume, and LVM is left-ventricular mass. MASS software (Medis Medical Imaging Systems, Leiden, the Netherlands) was used to process the images. End-diastolic and end-systolic endocardial borders were traced manually to measure the left ventricular cavity in each short-axis image. Portions of the papillary muscles in continuity with the left ventricular wall were included in the myocardial mass and excluded from the left ventricular volume. The software also permitted inclusion of the intracavitary papillary muscle components as needed. Measurements from each slice were summed by the method of disks. LVEF was calculated from the endocardial volumes:  $EF = 100(EDV - ESV)/EDV$ . Interobserver difference for left ventricular ESV was  $2.6 \pm 2.7$  mL, intraobserver difference was  $-2.7 \pm 0.4$  mL, and interscan variability was  $0.3 \pm 3.5$  mL. Interobserver difference for left ventricular EDV was  $-3.0 \pm 9.4$  mL, intraobserver difference was  $-2.7 \pm 3.2$  mL, and interscan variability was  $-2.3 \pm 8.9$  mL. Interobserver difference for LVEF was  $-4 \pm 4\%$ , intraobserver difference was  $1 \pm 1\%$ , and interscan variability was  $-1.3 \pm 2.5\%$ .

### Blood Pressure

Four measurements of blood pressure were obtained by use of a nonferromagnetic blood pressure cuff for the arm and a Welch Allyn automatic blood pressure monitor.<sup>11</sup> Measurements were taken (1) before the start of the scan outside the magnet, (2) before the scan with the patient inside the magnet, (3) after the scan with the patient inside the magnet, and (4) immediately after the scan with the patient outside the magnet. We averaged the blood pressure from measurements 2 and 3 ( $n=2355$ ) when both were available; otherwise, we used whichever of these 2 measurements was available ( $n=132$ ), we averaged measures 1 and 4 ( $n=63$ ), or we used either measure 1 or 4 ( $n=42$ ). Given the influence of blood pressure and afterload on LVEF, these blood pressure measurements obtained in proximity to the MRI scan were used in analysis rather than those obtained at a different time during the third clinic visit.<sup>11</sup>

### DEXA and Electron Beam-Computed Tomography

DEXA scans were performed with the use of a dual-beam absorption energy unit (Delphi W unit, Hologic, Inc, Bedford, Mass) bone densitometer in array mode with Oasis software to measure body

composition, including fat mass and fat-free mass.<sup>2</sup> Coronary artery calcium was measured with the use of an Imatron C-150XP electron beam-computed tomography (EBCT) scanner (Imatron, Inc, San Bruno, Calif). Presence of coronary artery calcium was defined as an EBCT score of  $>10$  Agatston units.<sup>12</sup>

### Study Definitions

Gender, ethnicity, and age were self-reported. Heavy alcohol use was defined as  $>255$  g of alcohol consumption per week, 2 standard deviations above the mean. Cocaine use was self-reported. Body surface area (BSA) was calculated with the use of gender-specific equations derived by Tikuisis et al.<sup>13</sup> Hypertension was defined as blood pressure  $\geq 140/90$  mm Hg or taking antihypertensive medication. Diabetes mellitus was defined as a fasting serum glucose  $\geq 126$  mg/dL, nonfasting serum glucose  $\geq 200$  mg/dL, or self-reported diabetes with use of hypoglycemic medication. History of myocardial infarction was determined by a yes answer to "Has a doctor or other health professional ever told you that you had a heart attack?" This includes myocardial infarction, coronary occlusion, or coronary thrombosis.<sup>14</sup> History of congestive heart failure was determined by a yes answer to "Has a doctor or other health professional ever told you that you have congestive heart failure, an enlarged heart, a weak heart, or cardiomyopathy?"

### Data Analysis

Baseline characteristics were compared between men and women by the Student *t* test for continuous variables and  $\chi^2$  test for discrete variables. Smoothed histograms of LVEF and left ventricular EDV or ESV (indexed to BSA) were constructed for each gender. The relationship of EDV and ESV with LVEF was found to be nonlinear, so we log-transformed ventricular volumes and logit-transformed LVEF. For similar reasons, we log-transformed stroke volume when we assessed its relationship with log EDV. To determine whether gender was associated with stroke volume independent of EDV, linear regression was performed with the dependent variable log stroke volume and independent variables of log EDV and gender. The *P* value associated with the  $\beta$  coefficient of the gender term was used to determine whether the intercept of the EDV-stroke volume relationship differed by gender. An interaction term (gender  $\times$  log EDV) was entered into this model to determine whether the slope of the EDV-stroke volume relationship also differed by gender. To determine whether our findings were independent of confounders, multivariable linear regression was performed (dependent variable, log stroke volume; independent variables, log EDV and gender) with the following covariates incorporated: mean arterial pressure, height, weight, and self-reported history of heart failure or myocardial infarction, diabetes mellitus, or alcohol or cocaine use. An interaction term (gender  $\times$  log EDV) was then entered into these models to determine whether there were slope differences between genders in the EDV-stroke volume relationship. A series of additional models was constructed with alternative potential confounders to determine the robustness of our conclusions. A similar series of models was constructed with log-transformed stroke work (stroke volume  $\times$  mean arterial pressure) as the dependent variable. Additionally, we performed a subgroup analysis excluding subjects with prior myocardial infarction, congestive heart failure, or positive coronary artery calcification (CAC) score ( $n=2060$ , including 1204 women and 856 men). We also performed a second subgroup analysis excluding only subjects with hypertension ( $n=1788$ , including 958 women and 830 men).

To establish gender-specific threshold values for low LVEF, we selected a healthy reference subpopulation ( $n=718$ , including 308 men and 410 women) from our overall study cohort by excluding participants with a body mass index  $>30$  kg/m<sup>2</sup>, those with a self-reported history of valvular heart disease, congenital heart disease, hypertension, heart failure, myocardial infarction, diabetes, or heavy alcohol or cocaine use, and those with left ventricular hypertrophy as measured by cardiac MRI (LVM,  $>89$  g/m<sup>2</sup> for women and  $>112$  g/m<sup>2</sup> for men) or CAC as measured by EBCT. A

**TABLE 1. Demographic Data and Clinical Characteristics of Men and Women in DHS Participants Aged 30 to 65 Years**

	Women (n=1435)	Men (n=1183)	P
Age, y	45±9	44±9	0.4
Body mass index, kg/m <sup>2</sup>	31.5±7.9	29.1±5.9	<0.001
BSA, m <sup>2</sup>	1.9±0.25	2.0±0.22	<0.001
Race/ethnicity			<0.001
Black	52	47	
White	29	34	
Hispanic	18	16	
Hypertension	33	30	0.06
Systolic blood pressure, mm Hg	125±18	129±16	<0.001
Diastolic blood pressure, mm Hg	78±10	79±10	0.2
Heart rate, bpm	77±11	75±12	<0.001
Cardiac output, L/min	5.3±1.4	5.7±1.4	<0.001
Cardiac index, L/min per m <sup>2</sup>	2.8±0.6	2.8±0.6	0.2
Left ventricular mass, g	141.3±33.8	191.7±44.4	<0.001
LVM/body surface area, g/m <sup>2</sup>	74.2±14.2	94.1±18.4	<0.001
LVM/fat-free mass, g/kg	3.0±0.5	3.0±0.6	0.7
Concentricity (LVM/EDV)	1.6±0.4	1.8±0.4	<0.001
CAC >10 Agatston units	14	27	<0.001
Diabetes	11.4	10.6	0.5
History of myocardial infarction	1.7	2.7	0.07
Congestive heart failure	2.6	2.2	0.5
Heavy alcohol use	1.8	7.2	<0.001
Self-reported cocaine use	9.6	18.4	<0.001
Past or present tobacco use	39	55	<0.001

All numbers are percentages for categorical variables or mean±SD for continuous variables.

gender-specific low LVEF was defined as being below the 2.5th percentile of women or men in this reference healthy subpopulation.

SUDAAN (Research Triangle Institute, Research Triangle Park, NC) was used to create population-weighted histograms of LVEF in male and female residents of Dallas County. For all other statistical analyses, SAS 9.13 (SAS Institute, Inc, Cary, NC) was used. A value of  $P<0.05$  was considered to be statistically significant.

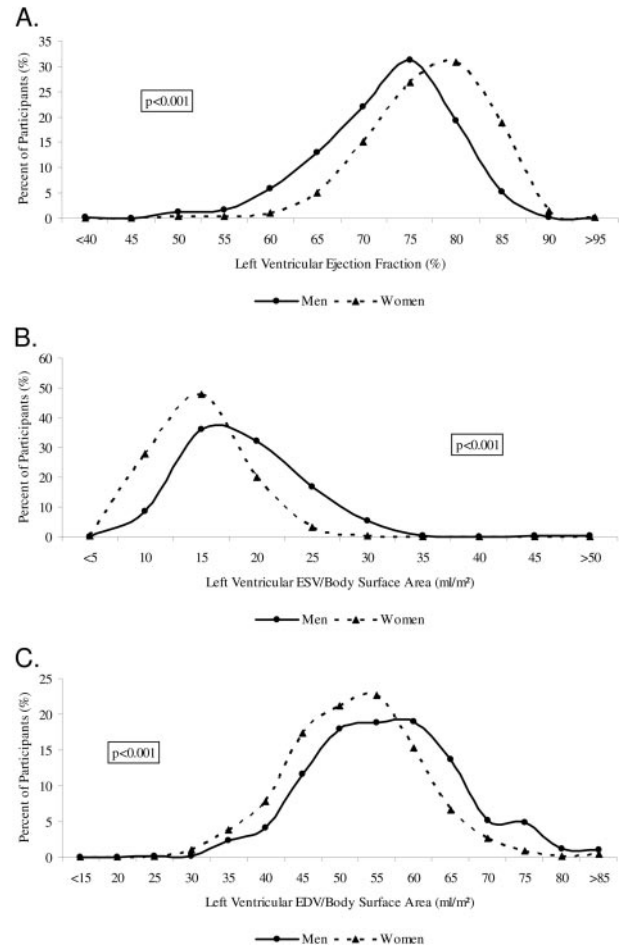
The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed to the article as written.

### Results

Baseline characteristics of women and men are presented in Table 1. Women were more likely than men to have a higher body mass index and heart rate and less likely than men to have detectable CAC or to report tobacco, heavy alcohol, or cocaine use. A larger percentage of women than men were black. There were no significant gender differences in cardiac index or history of heart failure or diabetes. LVM indexed to BSA and concentricity (LVM/EDV) were lower in women than in men, but LVM indexed to fat-free mass was the same for both genders.

### Comparing Ejection Fraction and Ventricular Volumes in Men and Women

The distribution of LVEF was shifted to the right (ie, higher LVEF) in women as compared with men (Figure 1A),

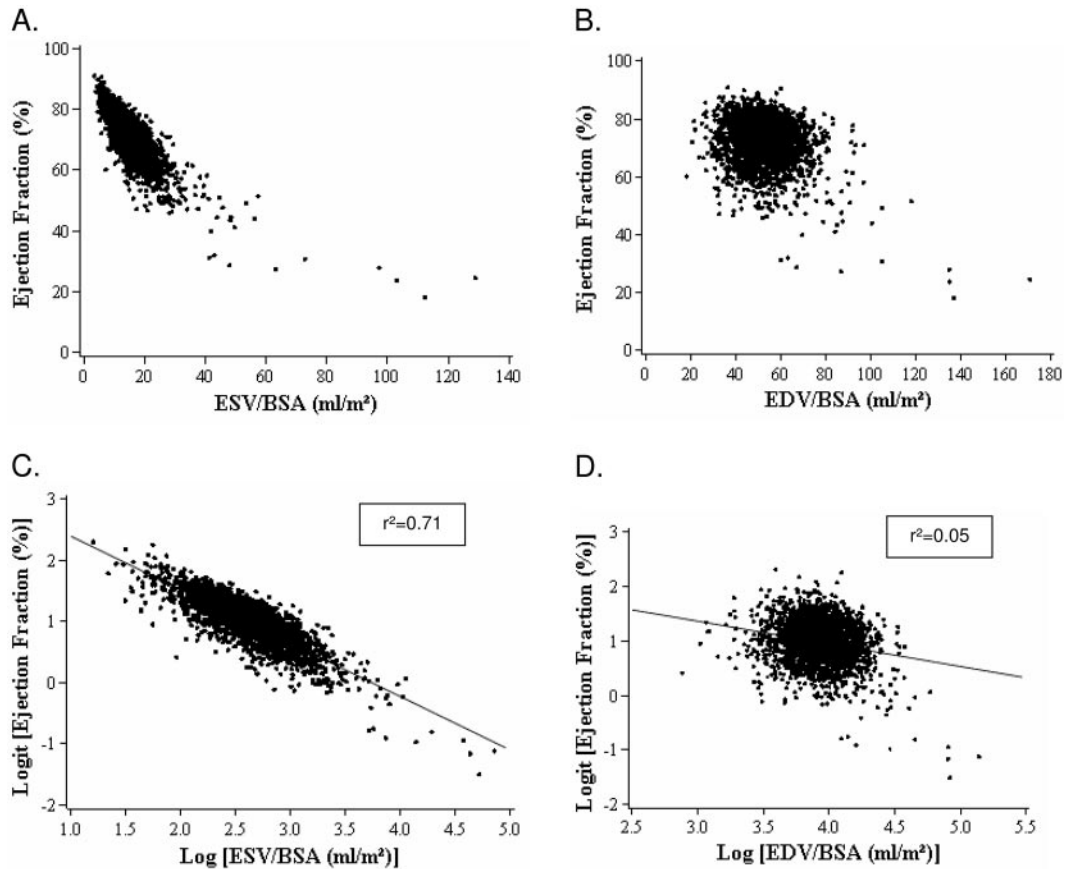


**Figure 1.** A, Histograms of LVEF by gender in Dallas County residents aged 30 to 65 years; B, left ventricular ESV/BSA; and C, left ventricular EDV/BSA.

whereas the distributions of left ventricular ESV indexed to BSA (Figure 1B) and EDV indexed to BSA (Figure 1C) were shifted to the left in women as compared with men (ie, lower volumes in women). The median (25th, 75th percentile) LVEF was 75% (70%, 79%) in women versus 70% (65%, 75%) in men ( $P<0.001$ ), and the median ESV indexed to BSA was 12 (9.7, 15) mL/m<sup>2</sup> in women versus 16 (13, 20) mL/m<sup>2</sup> in men ( $P<0.001$ ). Similarly, the median indexed EDV was smaller in women than in men: 49 (43, 55) mL/m<sup>2</sup> versus 54 (48, 61) mL/m<sup>2</sup>, respectively ( $P<0.001$ ). A low LVEF defined as below the 2.5th percentile of a healthy subset of the DHS was 61% in women and 55% in men.

### Relationship Between Left Ventricular Volumes and Ejection Fraction, Overall and by Gender

Scatterplots demonstrated that the relationships of indexed ESV (Figure 2A) or indexed EDV (Figure 2B) with LVEF were nonlinear. Log transformation of ventricular volume and logit transformation of LVEF, which improved the linear fit (especially for ESV), are shown for ESV (Figure 2C) and for EDV (Figure 2D). In both cases, an increased indexed left ventricular volume was associated with a decreased LVEF. However, the percentage of variation of LVEF explained by indexed ESV was substantially higher ( $r^2=0.71$ ,  $P<0.001$ )



**Figure 2.** Relationship between EF and ESV/BSA (A) or EDV/BSA (B). Because of a nonlinear relationship, we logit-transformed LVEF and log-transformed ESV/BSA (C) or EDV/BSA (D). The  $r^2$  value is the percentage of variation explained in logit EF by log ESV/BSA (C) or log EDV/BSA (D).

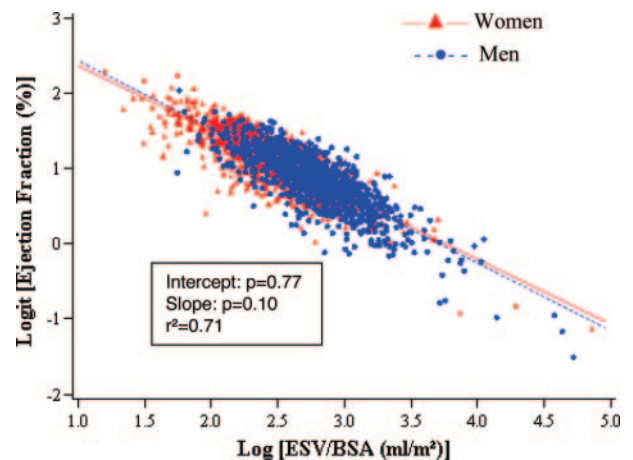
than that explained by indexed EDV ( $r^2=0.05$ ,  $P<0.001$ ). The relationship between ESV and LVEF in men and women overlapped (Figure 3), and in a gender-combined model, neither the intercept nor slope differed significantly between men and women, demonstrating that for any given ESV, men and women would have a comparable LVEF. Because of this finding and the poor correlation of EDV and LVEF (Figure 2D), we focused on comparing the relationship of EDV and stroke volume in men and women, reasoning that this analytic approach would be a more robust method to determine whether there were gender differences in LVEF independent of EDV (inasmuch as  $LVEF = \text{stroke volume} / EDV$ ).

**Relationship of EDV to Stroke Volume and Stroke Work in Men and Women**

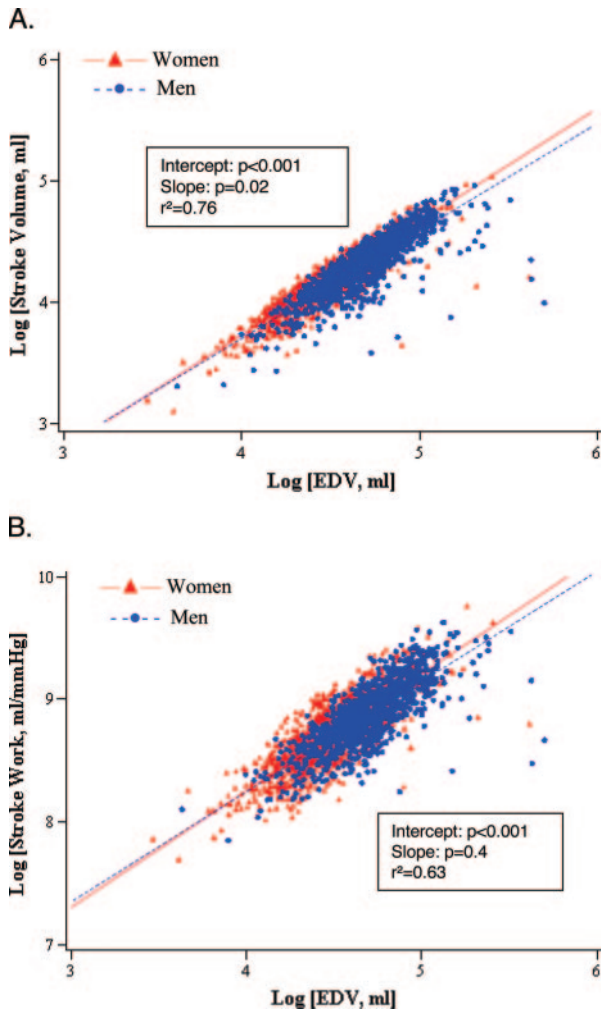
Log stroke volume and log EDV were highly correlated ( $r^2=0.76$ ,  $P<0.001$ ). For a given EDV, women had a higher stroke volume (leading to a smaller ESV and higher LVEF) than did men (Figure 4A). The intercept but not slope of the relationship of log stroke work (stroke volume  $\times$  mean arterial pressure) versus log EDV also differed significantly between women and men (Figure 4B).

The correlation of LVEF with blood pressure (either mean arterial pressure or systolic blood pressure) or with age was poor in men and women ( $r^2<0.01$  for all). In multivariable linear regression analysis, the EDV–stroke volume relation-

ship had a higher intercept and significantly different slope in women than in men, independent of other potential confounders (Table 2). To determine whether the association of gender and stroke volume was robust, a series of alternative multi-



**Figure 3.** EF versus ESV/BSA in the DHS by gender. As in Figure 2, logit-transformed LVEF and log-transformed ESV/BSA were used. The intercept  $P$  value refers to the  $P$  value from the gender coefficient in the model with logit LVEF as the dependent variable and log ESV/BSA and gender as independent variables. The slope  $P$  value refers to the  $P$  value associated with the interaction term (gender  $\times$  log ESV/BSA) added to the above model.



**Figure 4.** Log stroke volume (SV) versus log EDV (A) or log stroke work (SV × mean arterial pressure) versus log EDV (B) in the DHS by gender. The intercept *P* value refers to the *P* value from the gender coefficient in the model with log SV (A) or log stroke work (B) as the dependent variable and log EDV and gender as independent variables. The slope *P* value refers to the *P* value associated with the interaction term (gender × log EDV) added to the above models.

variable regression models were constructed in which the following covariates were substituted: CAC for myocardial infarction; body mass index, BSA, or fat mass and fat-free mass for height and weight; and systolic blood pressure or pulse pressure for mean arterial pressure. In each case, the slope and intercept of the EDV–stroke volume relationship remained significantly different in men and women ( $P < 0.05$  for various slopes, except  $P = 0.06$  when fat mass and fat-free mass were substituted for height and weight). In subgroup analysis excluding participants with myocardial infarction, congestive heart failure, and positive CAC score as well as in subgroup analysis excluding for hypertension, the EDV–stroke volume relationship had a higher intercept in women than men ( $P < 0.001$ ), but there was no significant slope difference. The slope of the relationship between log stroke work and EDV (Figure 4B) remained the same in women and men in multivariable analysis ( $P = 0.9$ ).

As crude indexes of contractility, we divided systolic blood pressure by ESV indexed to BSA. This ratio was significantly higher in women than in men ( $3.3 \pm 1.6$  versus  $2.1 \pm 0.9$  mm Hg/mL per  $m^2$ , respectively;  $P < 0.001$ ). The gender difference in this ratio persisted whether ESV was not indexed or indexed to fat-free mass or height<sup>27</sup>. We also divided stroke work (stroke volume × mean arterial pressure) by EDV to give a single point estimate of preload recruitable stroke work. This ratio was also significantly higher in women than in men ( $73 \pm 12$  versus  $69 \pm 12$  mm Hg,  $P < 0.001$ ).

### Discussion

It is increasingly recognized that women manifest cardiovascular disease in ways different from men.<sup>14</sup> Understanding these differences will undoubtedly be important to provide optimal care to patients of both genders. In a large probability-based sample of Dallas County residents aged 30 to 65 years, women had a higher LVEF and smaller left ventricular EDV and ESV than did men, as assessed by cardiac MRI, arguably the “gold standard” imaging modality for such purposes. Gender differences in ESV accounted for the differences in LVEF, emphasizing the importance of stroke volume for any given EDV. In multivariable analysis, female gender was associated with a higher stroke volume despite adjustment for EDV and other potential confounders. Additionally, the threshold value to define a low LVEF was 6 LVEF points higher in women (61%) than in men (55%). Thus, for EFs at the lower limits of normal, there may be more depression in contractile function in women than previously appreciated. Whether this difference is sufficient to explain the development of frank heart failure is not clear but deserves further investigation. Furthermore, these data suggest that gender-specific LVEF criteria may be necessary in clinical decision-making, such as when patients with heart failure are classified into those with preserved or reduced LVEF and when a decision is being made whether to implant an automatic cardiac defibrillator, although this provocative idea needs to be tested in clinical trials.

Others have used echocardiography to address whether the LVEF differs in women and men. Early studies of small cohorts have shown LVEF to be higher in women than in men,<sup>15</sup> with some finding gender differences in fractional shortening only in subjects over 55 years of age.<sup>16</sup> A more recent study from Brazil has reported that EF is not different in men and women.<sup>17</sup> In contrast, most studies with larger cohorts have shown that the prevalence of systolic dysfunction (ie, low LVEF) is more than 2-fold higher in men than in women.<sup>3,18–22</sup> Additionally, the mean LVEF in women has been found to be 1% to 5% higher<sup>3–6</sup> and to persist in multivariable models.<sup>3,4,6</sup>

LVEF in men and women has also been compared by cardiac MRI. Some studies have reported LVEF to be  $\approx 3$  EF points higher in women than men,<sup>23,24</sup> but others have reported that the EF is similar in both genders.<sup>7,8</sup> In the Framingham Heart Offspring Study, the largest MRI study (63 men and 79 women) of which we are aware,<sup>9</sup> there were no significant differences in LVEF between men (69%) and women (70%).

**TABLE 2. Multivariable Linear Regression Analysis**

Dependent Variable: Log Stroke Volume	Unadjusted*			Adjusted†		
	$\beta$ (Female)	P	Interaction P	$\beta$ (Female)	P	Interaction P
All subjects (n=2618)	0.06	<0.001	0.02	0.04	<0.001	0.03
Excluding MI, CHF, and CAC (n=2060)	0.06	<0.001	0.4	0.04	<0.001	0.5
Excluding hypertensive subjects (n=1788)	0.05	<0.001	0.9	0.04	<0.001	0.9

MI indicates myocardial infarction; CHF, congestive heart failure.

\*In unadjusted models,  $\beta$  coefficient female is derived from the model with gender and log EDV. The interaction term is from the same model with the interaction term (gender $\times$ log EDV) incorporated. When the interaction term was included in the model for all subjects,  $\beta$  coefficient female was  $-0.15$  ( $P=0.09$ ). For unadjusted model,  $r^2=0.77$  for log stroke volume.

†The following were included as covariates in the adjusted models: log EDV, log age, log mean arterial pressure, log heart rate, log height, log weight, CHF, diabetes mellitus, MI, heavy alcohol use, cocaine use, and tobacco use. All models were adjusted for all of these confounders except when the variable was one of the exclusions for the subgroup. When the interaction term was included in model for all subjects,  $\beta$  coefficient female was  $-0.16$  ( $P=0.08$ ). For adjusted model,  $r^2=0.80$  for log stroke volume.

When purported gender differences in LVEF are assessed, it is also important to consider the impact of gender differences in ventricular volume. By use of pressure-volume loop analysis in a study of 30 subjects, women were shown to have higher left ventricular systolic function independent of ventricular volume.<sup>25</sup> In a study of 517 subjects, the mean LVEF was higher in women than in men by 1 (hypertensive) or 2 (normotensive) LVEF percentage points. Accounting for body size decreased differences in systolic function in normotensive but not hypertensive individuals.<sup>26</sup> We found that the differences in stroke volume between men and women were independent of differences in ventricular EDV and body size.

Women, as compared with men, are overrepresented among patients with heart failure who have a preserved LVEF.<sup>1</sup> The basis of this observation is not yet well understood. Interestingly, the right-shifted distribution of LVEF in female, as compared with male, patients with heart failure demonstrated in the EuroHeart Survey<sup>27</sup> is similar to our findings in the general population (Figure 1). Women whose LVEF falls in the range between the male and female gender-specific criteria for low LVEF (eg, in the present study, between 55% and 61%) would be misclassified as having a preserved LVEF, when in fact their LVEF is reduced. In the EuroHeart Survey,<sup>27</sup>  $\approx 10\%$  of women with heart failure would have their classification changed from heart failure with preserved LVEF to reduced LVEF if the LVEF threshold criteria for women were increased from 55% to 60%. We recognize that other mechanisms besides misclassification are undoubtedly operative for the association of female gender and heart failure with a preserved LVEF.

The higher stroke volumes in women than in men for a given EDV were likely due to either higher contractility or lower afterload. Findings consistent with the latter were that women versus men had lower blood pressures, that the stroke volume differences between the genders were no longer significant when subjects with hypertension were excluded (Table 2), and that the slope of the stroke work versus EDV relationship was the same in women and men (Figure 4B). In contrast, there were other data supporting the contention that contractility was higher in women than in men, including a higher systolic blood pressure/ESV ratio,<sup>28</sup> a higher stroke work/EDV ratio, and persistence of higher stroke volume for

a given EDV in multivariable analysis that adjusted for blood pressure, although the utility of these indexes as measured in a population-based study is uncertain. The possibility that the genders differ in cardiac contractility and response to cardiovascular stress has been well documented previously, including elegant studies of patients with aortic stenosis in which women had a higher LVEF and were less likely to have low LVEF than men.<sup>29</sup> A variety of animal studies also suggest that male versus female animals were more likely to develop cardiac dysfunction and/or ventricular dilation in response to stress, including pressure overload.<sup>30–37</sup> Nevertheless, the data in the present study do not allow us to determine with certainty whether the higher stroke volume for a given EDV in women versus men was secondary to differences in contractile state or loading conditions.

### Limitations of the Study

Although interpretation of cardiac MRI was performed in absence of knowledge of other study information and typically performed with the use of 150% to 200% magnification centered on the heart, structures outside the heart could not be totally masked, and this may have led to an unintentional bias in interpretation. Also, we cannot exclude the possibility of residual confounding in the association of gender and LVEF. In particular, hematocrit was not measured, and the effect of anemia in premenopausal women in contributing to the observed gender LVEF differences is therefore unknown. The poor correlation of LVEF with age, which would reflect menopausal status, and the similar cardiac index between men and women suggest that anemia is unlikely to be the major explanation of our findings. LVEF is load dependent and is not an intrinsic measure of contractility. Nevertheless, LVEF is widely used in making therapeutic decisions; thus, the gender differences in LVEF demonstrated in the present study have clinical relevance irrespective of their underlying cause. The ascertainment of a healthy reference subpopulation to define a low LVEF may have been biased by differential reporting of medical illness by women and men, although the exclusions of subjects with left ventricular hypertrophy by MRI or CAC by EBCT should have reduced this bias. We were unable to calculate ventricular stress in the absence of measured ventricular dimensions in the DHS. LVEF was assessed with

cardiac MRI, and our conclusions may not be applicable to assessments by other imaging modalities.

**Conclusions**

In the general population of Dallas County, women had higher LVEF than did men, reflecting a higher stroke volume for a given EDV. This difference in stroke volume was independent of potential confounders and may reflect underlying gender differences in native cardiac function or response to hemodynamic stress. These data raise the provocative concept of whether gender-specific criteria are needed in clinical decision making, with use of a threshold of ≈5 LVEF points higher in women than in men. Furthermore, these data suggest that women with LVEF toward the lower limits of normal have more severe contractile dysfunction than previously appreciated and that this may be an explanation for their apparent predisposition to develop symptomatic heart failure.

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**Disclosures**

None.

**References**

1. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol.* 2004;43:317–327.
2. Drazner MH, Dries DL, Peshock RM, Cooper RS, Klassen C, Kazi F, Willett D, Victor RG. Left ventricular hypertrophy is more prevalent in blacks than whites in the general population: the Dallas Heart Study. *Hypertension.* 2005;46:124–129.
3. Devereux RB, Roman MJ, Paranicas M, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Rodeheffer RJ, Cowan LD, Howard BV. A population-based assessment of left ventricular systolic dysfunction in middle-aged and older adults: the Strong Heart Study. *Am Heart J.* 2001;141:439–446.
4. Gerds E, Zabalgoitia M, Bjornstad H, Svendsen TL, Devereux RB. Gender differences in systolic left ventricular function in hypertensive patients with electrocardiographic left ventricular hypertrophy. *Am J Cardiol.* 2001;87:980–983.
5. Luchner A, Brockel U, Muscholl M, Hense HW, Doring A, Riegger GA, Schunkert H. Gender-specific differences of cardiac remodeling in subjects with left ventricular dysfunction: a population-based study. *Cardiovasc Res.* 2002;53:720–727.
6. Wong ND, Gardin JM, Kurosaki T, Anton-Culver H, Sidney S, Roseman J, Gidding S. Echocardiographic left ventricular systolic function and volumes in young adults: distribution and factors influencing variability. *Am Heart J.* 1995;129:571–577.
7. Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. *J Magn Reson Imaging.* 2003;17:323–329.
8. Lorenz CH, Walker ES, Morgan VL, Klein SS, Graham TP Jr. Normal human right and left ventricular mass, systolic function, and gender differences by cine magnetic resonance imaging. *J Cardiovasc Magn Reson.* 1999;1:7–21.
9. Salton CJ, Chuang ML, O'Donnell CJ, Kupka MJ, Larson MG, Kissinger KV, Edelman RR, Levy D, Manning WJ. Gender differences and normal left ventricular anatomy in an adult population free of hypertension: a cardiovascular magnetic resonance study of the Framingham Heart Study Offspring cohort. *J Am Coll Cardiol.* 2002;39:1055–1060.
10. Myerson SG, Bellenger NG, Pennell DJ. Assessment of left ventricular mass by cardiovascular magnetic resonance. *Hypertension.* 2002;39:750–755.

11. Victor RG, Haley RW, Willett DL, Peshock RM, Vaeth PC, Leonard D, Basit M, Cooper RS, Iannacchione VG, Visscher WA, Staab JM, Hobbs HH. The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. *Am J Cardiol.* 2004;93:1473–1480.
12. Jain T, Peshock R, McGuire DK, Willett D, Yu Z, Vega GL, Guerra R, Hobbs HH, Grundy SM. African Americans and Caucasians have a similar prevalence of coronary calcium in the Dallas Heart Study. *J Am Coll Cardiol.* 2004;44:1011–1017.
13. Tikuisis P, Meunier P, Jubenville CE. Human body surface area: measurement and prediction using three dimensional body scans. *Eur J Appl Physiol.* 2001;85:264–271.
14. Jacobs AK, Eckel RH. Evaluating and managing cardiovascular disease in women: understanding a woman's heart. *Circulation.* 2005;111:383–384.
15. Buonanno C, Arbustini E, Rossi L, Dander B, Vassanelli C, Paris B, Poppi A. Left ventricular function in men and women: another difference between sexes. *Eur Heart J.* 1982;3:525–528.
16. de Simone G, Devereux RB, Roman MJ, Ganau A, Chien S, Alderman MH, Atlas S, Laragh JH. Gender differences in left ventricular anatomy, blood viscosity and volume regulatory hormones in normal adults. *Am J Cardiol.* 1991;68:1704–1708.
17. Schwartzman PR, Fuchs FD, Mello AG, Coli M, Schwartzman M, Moreira LB. Normal values of echocardiographic measurements: a population-based study. *Arq Bras Cardiol.* 2000;75:107–114.
18. Davies M, Hobbs F, Davis R, Kenkre J, Roalfe AK, Hare R, Wosornu D, Lancashire RJ. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet.* 2001;358:439–444.
19. McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, Dargie HJ. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet.* 1997;350:829–833.
20. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE. Prevalence of heart failure and left ventricular dysfunction in the general population: the Rotterdam Study. *Eur Heart J.* 1999;20:447–455.
21. 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.
22. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation.* 2003;108:977–982.
23. Marcus JT, DeWaal LK, Gotte MJ, van der Geest RJ, Heethaar RM, Van Rossum AC. MRI-derived left ventricular function parameters and mass in healthy young adults: relation with gender and body size. *Int J Card Imaging.* 1999;15:411–419.
24. Sandstede J, Lipke C, Beer M, Hofmann S, Pabst T, Kenn W, Neubauer S, Hahn D. Age- and gender-specific differences in left and right ventricular cardiac function and mass determined by cine magnetic resonance imaging. *Eur Radiol.* 2000;10:438–442.
25. Hayward CS, Kalnins WV, Kelly RP. Gender-related differences in left ventricular chamber function. *Cardiovasc Res.* 2001;49:340–350.
26. Celentano A, Palmieri V, Arezzi E, Mureddu GF, Sabatella M, Di Minno G, De Simone G. Gender differences in left ventricular chamber and midwall systolic function in normotensive and hypertensive adults. *J Hypertens.* 2003;21:1415–1423.
27. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J. The EuroHeart Failure survey programme: a survey on the quality of care among patients with heart failure in Europe, part 1: patient characteristics and diagnosis. *Eur Heart J.* 2003;24(pt 1):442–463.
28. Nivatpumin T, Katz S, Scheuer J. Peak left ventricular systolic pressure/end-systolic volume ratio: a sensitive detector of left ventricular disease. *Am J Cardiol.* 1979;43:969–974.
29. Carroll JD, Carroll EP, Feldman T, Ward DM, Lang RM, McGaughey D, Karp RB. Sex-associated differences in left ventricular function in aortic stenosis of the elderly. *Circulation.* 1992;86:1099–1107.
30. Weinberg EO, Thienelt CD, Katz SE, Bartunek J, Tajima M, Rohrbach S, Douglas PS, Lorell BH. Gender differences in molecular remodeling in pressure overload hypertrophy. *J Am Coll Cardiol.* 1999;34:264–273.
31. Douglas PS, Katz SE, Weinberg EO, Chen MH, Bishop SP, Lorell BH. Hypertrophic remodeling: gender differences in the early response to left ventricular pressure overload. *J Am Coll Cardiol.* 1998;32:1118–1125.

32. Olsson MC, Palmer BM, Leinwand LA, Moore RL. Gender and aging in a transgenic mouse model of hypertrophic cardiomyopathy. *Am J Physiol*. 2001;280:H1136–H1144.
33. Gardner JD, Brower GL, Janicki JS. Gender differences in cardiac remodeling secondary to chronic volume overload. *J Card Fail*. 2002;8:101–107.
34. Sharkey LC, Holycross BJ, Park S, McCune SA, Hoversland R, Radin MJ. Effect of ovariectomy in heart failure-prone SHHF/Mcc-facp rats. *Am J Physiol*. 1998;275:R1968–R1976.
35. Litwin SE, Katz SE, Litwin CM, Morgan JP, Douglas PS. Gender differences in postinfarction left ventricular remodeling. *Cardiology*. 1999;91:173–183.
36. Jain M, Liao R, Podesser BK, Ngoy S, Apstein CS, Eberli FR. Influence of gender on the response to hemodynamic overload after myocardial infarction. *Am J Physiol*. 2002;283:H2544–H2550.
37. Schwertz DW, Buttrick PM. Gender influences on myocardial structure and function. In: Douglas PS, ed. *Cardiovascular Health and Disease in Women*. Vol 2. Philadelphia, Pa: WB Saunders, 2002:426–444.

### CLINICAL PERSPECTIVE

In the present study of 2618 subjects of the Dallas Heart Study, we found that the left ventricular ejection fraction (LVEF) as measured by cardiac magnetic resonance imaging was higher in women than in men and that this difference was independent of potential confounders, including ventricular volume. A low LVEF, defined as below the 2.5th percentile of a healthy subgroup of the overall cohort, was 6 LVEF points higher in women (<61%) than in men (<55%). These data suggest that women with LVEF at the lower limits of normal, eg, 55% to 60%, may in fact have more systolic dysfunction than previously appreciated. Additionally, these data raise the provocative question of whether gender-specific LVEF thresholds are needed in clinical decision-making, with a threshold  $\approx$ 5 LVEF points higher in women than in men, an approach that would need to be tested in future studies.