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Left Ventricular Function

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

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OBJECTIVES We sought to derive gender-specific cardiovascular magnetic resonance (CMR) reference values for normative left ventricular (LV) anatomy and function in a healthy adult population of clinically relevant age.

BACKGROUND Cardiovascular magnetic resonance imaging is increasingly applied in the clinical setting, but age-relevant, gender-specific normative values are currently unavailable.

METHODS A representative sample of 318 Framingham Heart Study (FHS) Offspring participants free of clinically overt cardiovascular disease underwent CMR examination to determine LV end-diastolic and end-systolic volume (EDV and ESV, respectively), mass, ejection fraction (EF) and linear dimensions (wall thickness, cavity length). Subjects with a clinical history of hypertension or those with a systolic blood pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg at any FHS cycle examination were excluded, leaving 142 subjects (63 men, 79 women; age 57 ± 9 years).

RESULTS All volumetric (EDV, ESV, mass) and unidimensional measures were significantly greater ($p < 0.001$) in men than in women and remained greater ($p < 0.02$) after adjustment for subject height. Volumetric measures were greater ($p < 0.001$) in men than in women after adjustment for body surface area (BSA), but there were increased linear dimensions in women after adjustment for BSA. In particular, end-diastolic dimension indexed to BSA was greater in women ($p < 0.001$) than in men. There were no gender differences in global LVEF (men = 0.69; women = 0.70).

CONCLUSIONS Cardiovascular magnetic resonance measures of LV volumes, mass and linear dimensions differ significantly according to gender and body size. This study provides gender-specific normal CMR reference values, uniquely derived from a population-based sample of persons free of cardiovascular disease and clinical hypertension. These data may serve as a reference to identify LV pathology in the adult population. (J Am Coll Cardiol 2002;39:1055–60)

Normative reference values for left ventricular (LV) anatomy and function are important for accurate identification of disease, risk stratification and selection of therapy (1–4). Cardiovascular magnetic resonance (CMR) imaging allows accurate, unbiased determination of LV anatomy and function without geometric assumptions regarding ventricular shape (5). It also provides high spatial and temporal resolution and does not expose patients to potentially harmful ionizing radiation, making it ideal for serial assessments. Reference standards for LV anatomy and function derived using other invasive or noninvasive imaging modalities may not be appropriate for values measured from CMR data (6,7). Furthermore, because CMR is increasingly used for clinical assessment of LV size, function and mass, specific CMR-derived reference values are desirable. Age-appropriate reference standards are particularly important for identification of disease; however, prior reports of CMR reference values typically have employed young adult volunteers (8,9) or have been derived from relatively small sample sizes. Another factor in establishing normal reference values is gender differences in LV structure, which becomes particularly relevant with increasing age (10,11). Thus, we sought to determine CMR reference values for LV size, function and mass in a large, longitudinally followed, population-based cohort of middle-aged and older men and women free of clinically overt cardiovascular disease. The closely monitored Offspring cohort of the Framingham Heart Study (FHS), initiated in 1971, represents an appropriate sample in which cardiovascular disease,

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Abbreviations and Acronyms

BMI = body mass index
BSA = body surface area
CMR = cardiovascular magnetic resonance
ECG = electrocardiogram
EDD = end-diastolic dimension
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
FHS = Framingham Heart Study
IVS = interventricular septum thickness
LV = left ventricular
PWT = posterior wall thickness

hypertension and valvular heart disease can be excluded, making it uniquely suitable for determination of CMR reference values in the adult population.

METHODS

Subjects. The study design and selection criteria for the FHS Offspring study have been described previously (12). Adult participants in the FHS Offspring cohort who live in Massachusetts or a contiguous state were recruited to undergo CMR imaging using a random sampling strategy to recruit from strata of gender, decade age and quintile of Framingham coronary disease risk score (13). Using this sampling strategy, a representative sample of 318 subjects was recruited. Potential subjects were excluded if there were contraindications to CMR imaging, including pacemaker, implanted cardiodefibrillator, metallic intraocular or intracranial clips, history of foreign ocular bodies or claustrophobia. Participants with known chronic atrial fibrillation were also excluded. A total of 318 subjects underwent CMR imaging; all were free of clinically apparent cardiovascular disease, including angina and myocardial infarction. For the purpose of establishing reference values, we subsequently excluded subjects with a clinical history of hypertension, those taking an antihypertensive medication during any FHS cycle examination visit, or those with a resting systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg (14) during any FHS examination. The study was approved by human study committees of both the Boston University School of Medicine and Beth Israel Deaconess Medical Center. Written informed consent was obtained from all participants.

Imaging. Cardiovascular magnetic resonance imaging was performed with subjects positioned supine in a 1.5-T scanner using a 5-element cardiac array coil for radiofrequency signal detection (Gyroscan ACS/NT, Philips Medical Systems, Best, The Netherlands). Following scout images to determine the position and orientation of the heart within the thorax, images were acquired using a prospective, electrocardiogram (ECG)-triggered K-space segmented hybrid gradient-echo echo-planar breath-hold cine sequence (15). A stack of 10-mm thick contiguous slices encompassing the left ventricle from base to apex in the cardiac short-axis orientation was acquired during a series of end-tidal breath-holds. Imaging parameters included the following: repetition time = R-R interval, echo time = 9 ms, flip angle = 30°, effective temporal resolution of 39 ms. In-plane spatial resolution was 1.25×2.0 mm^2.

Image analysis. All image analysis was performed by an observer blinded to all clinical history (including age and gender) using a commercially available EasyScil workstation (Philips Medical Systems). Endocardial LV borders were manually traced at end-diastole (the first image in the ECG-gated cine dataset) and at end-systole (the cardiac phase with minimal cross-sectional area) (Fig. 1). In the tracing convention used, the papillary muscles were included as part of LV cavity volume. Left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were determined using a summation of disks ("Simpson's Rule") method. Ejection fraction (EF) was computed as EF = (EDV − ESV)/EDV. Left ventricular epicardial borders were also traced on the end-diastolic images with LV mass computed as the end-diastolic myocardial volume (i.e., epicardial − endocardial volumes) multiplied by myocardial density (1.05 g/ml). Intraobserver and interobserver reproducibility for LV volumetric measures by our group have been previously reported (16). In addition to volumetric measurements, one-dimensional measurements of LV end-diastolic dimension (EDD), posterior wall thickness (PWT) and anterior interventricular septum thickness (IVS) were measured from an end-diastolic short-axis slice immediately basal to the tips of the papillary muscles. Finally, end-diastolic LV long-axis lengths, from the apical endocardial border to the mitral valve plane, were measured from both the two-chamber and four-chamber data sets.

Statistical analysis. Descriptive anthropomorphic characteristics are presented by gender, with continuous variables summarized as mean ± 1 SD. Left ventricular volume, mass and linear dimensions are presented by gender as mean values and 95th percentile upper limits; between-gender differences were assessed using Student *t* tests. Whole-group and gender-specific regression analyses were performed to investigate the relations between LV parameters and height and calculated body surface area (BSA) (17), which were summarized using Pearson correlation. Height and weight were measured during subjects' contemporaneous FHS examinations. Further analyses of LV parameters were conducted after adjustment for subject height (m) and BSA (m^2).

RESULTS

Of the 318 FHS subjects who underwent CMR imaging, 176 were excluded for hypertension, leaving 142 subjects (63 men, 79 women) for determination of normative data. Clinical characteristics for this group are presented by gender in Table 1. Image quality was deemed not adequate for analysis in 5 (3.5%) of 142 subjects; unacceptable image quality was due primarily to subject difficulties in perform-

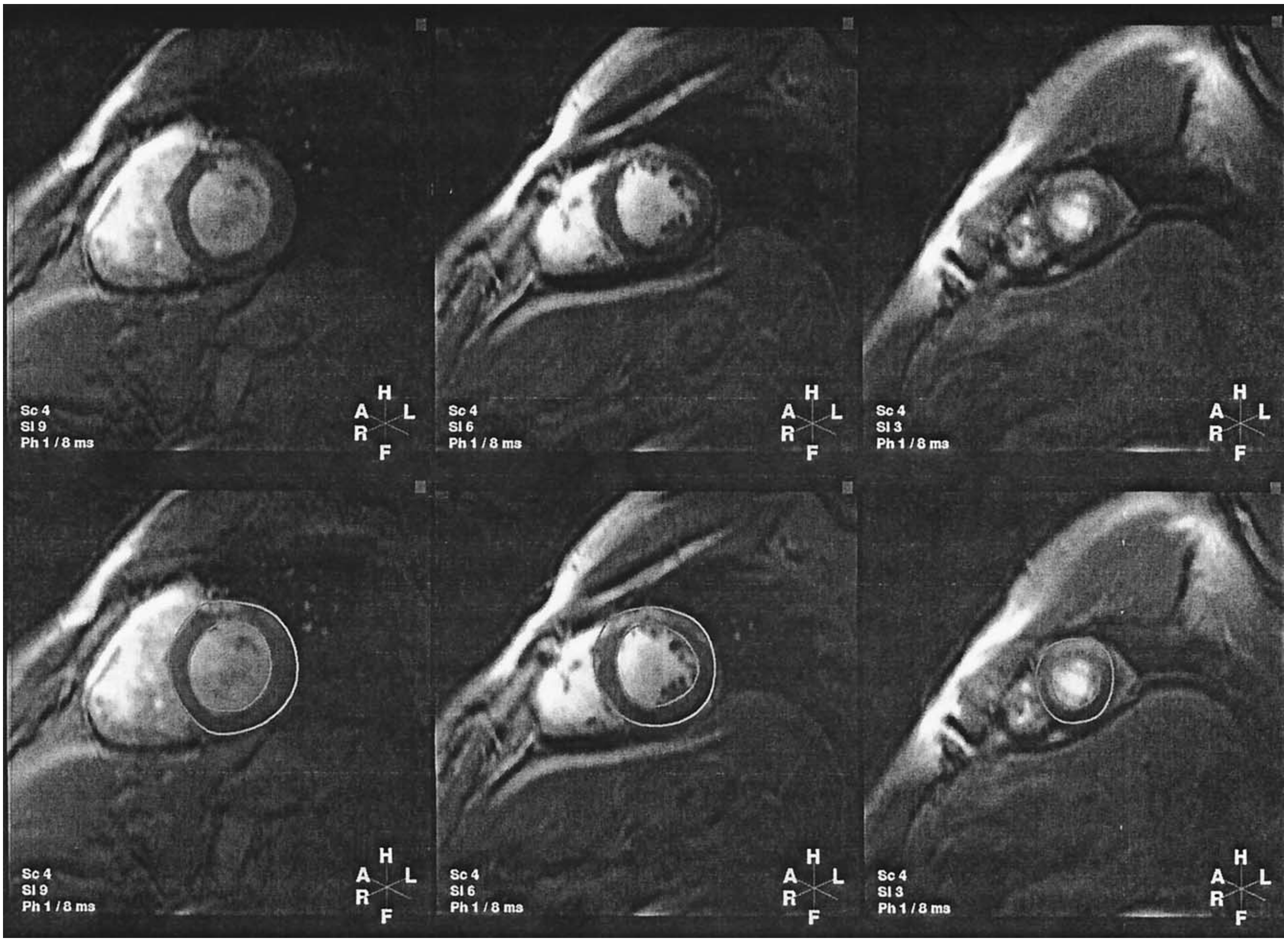

Figure 1. Representative double-oblique short-axis images at the basal **(left column)**, mid **(middle column)** and apical **(right column)** left ventricular levels, demonstrating the delineation of endocardial and epicardial borders.

ing 10- to 15-second end-tidal breath-holds. Mean values and 95th percentile upper limits for LV mass, EDV, ESV, EF and linear dimensions based on 137 subjects are presented by gender in Table 2. The 5th percentile (lower) limits for EF were 0.59 for men and 0.60 for women.

Table 1. Descriptive Characteristics of Subjects

Variable	Mean	SD	Minimum	Maximum
Men (n = 63)				
Age (yr)	56.7	9.1	38	72
SBP (mm Hg)	116.3	12.0	92	139
DBP (mm Hg)	72.5	7.7	56	88
Height (m)	1.75	0.06	1.63	1.92
Weight (kg)	85.1	15.8	54.4	130.6
BMI (kg/m^2)	27.8	4.91	19.7	43.2
BSA (m^2)	2.00	0.18	1.60	2.47
Women (n = 79)				
Age (yr)	57.7	9.5	36	78
SBP (mm Hg)	115.2	11.9	90	137
DBP (mm Hg)	70.6	8.3	53	86
Height (m)	1.62	0.06	1.48	1.77
Weight (kg)	65.7	14.4	42.6	123.4
BMI (kg/m^2)	25.0	5.0	18.4	46.0
BSA (m^2)	1.69	0.18	1.35	2.24

BMI = body mass index, BSA = body surface area, DBP = diastolic blood pressure, SBP = systolic blood pressure.

Except for EF, all unadjusted LV parameters were significantly greater in men than in women ($p < 0.001$).

In the pooled group of men and women, LV EDV, ESV, mass and linear dimensions each correlated significantly with height ($r = 0.38$ to 0.69, $p < 0.001$ for all) and BSA ($r = 0.41$ to 0.78, $p < 0.001$ for all), indicating that adjustment for body size is warranted. Apart from EDD, significant gender differences persisted after adjustment for subject height (Table 2). After adjustment for BSA (Table 2), volumetric variables (LV mass, EDV, ESV) remained significantly greater ($p < 0.001$) in men than in women, but EDD and two-chamber long-axis length were significantly greater in women than in men ($p < 0.001$), with a trend ($p < 0.09$) toward greater PWT, IVS and four-chamber length in women.

DISCUSSION

In this sample of healthy subjects from the prospective FHS Offspring cohort who were free of hypertension and symptomatic cardiovascular disease, we define normative CMR reference values for LV anatomy and global systolic function. There is increasing interest in and application of CMR

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Table 2. Means and 95% Upper Limits for Raw, Height-Adjusted, and BSA-Adjusted LV Variables

	Raw				
	Men		Women		
Variables	Mean	95% Upper Limit	Mean	95% Upper Limit	p Value*
LV mass (g)	155.1	201.4	103.0	134.0	0.0001
LV EDV (ml)	114.9	169.0	84.4	116.5	0.0001
LV ESV (ml)	36.3	65.0	25.1	40.9	0.0001
PWT (mm)	9.9	11.2	8.7	9.8	0.0001
IVS (mm)	10.1	11.7	8.9	10.1	0.0001
EDD (mm)	50.2	58.5	45.6	51.1	0.0001
2-ChL (mm)	82.3	93.8	73.2	83.7	0.0001
4-ChL (mm)	81.9	93.0	71.7	81.5	0.0001
LV EF	0.69	0.77	0.70	0.79	0.1019

	Raw/Height				
	Men		Women		
Variables	Mean	95% Upper Limit	Mean	95% Upper Limit	p Value*
LV mass (g/m)	88.6	114.0	63.6	81.9	0.0001
LV EDV (ml/m)	65.6	93.6	52.1	70.3	0.0001
LV ESV (ml/m)	20.7	35.5	15.5	24.5	0.0001
PWT (mm/m)	5.6	6.5	5.4	6.1	0.0013
IVS (mm/m)	5.8	6.9	5.5	6.4	0.0134
EDD (mm/m)	28.7	33.1	28.2	31.8	0.1616
2-ChL (mm/m)	47.1	52.1	45.1	49.8	0.0009
4-ChL (mm/m)	46.9	53.0	44.3	49.3	0.0001

	Raw/BSA				
	Men		Women		
Variables	Mean	95% Upper Limit	Mean	95% Upper Limit	p Value*
LV mass (g/m^2)	77.9	95.0	60.8	74.7	0.0001
LV EDV (ml/m^2)	57.6	79.5	49.8	65.5	0.0001
LV ESV (ml/m^2)	18.1	30.8	14.8	24.0	0.0001
PWT (mm/m^2)	5.0	6.0	5.2	6.3	0.0523
IVS (mm/m^2)	5.1	6.2	5.3	6.4	0.0564
EDD (mm/m^2)	25.3	29.7	27.1	31.8	0.0004
2-ChL (mm/m^2)	41.3	46.8	43.5	48.4	0.0005
4-ChL (mm/m^2)	41.5	47.7	42.7	47.8	0.0867

*p Values are from the test of difference in means between genders for each of the LV variables.
ChL = chamber length; EDD = end diastolic dimension; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; IVS = inter-ventricular septum thickness; LV = left ventricle; PWT = posterior wall thickness

imaging for clinical evaluation and epidemiologic study of LV structure and function. Thus, CMR-specific reference standards for LV anatomy and systolic function are needed for identification of disease, risk stratification and monitoring of the effects of therapy. The principal challenges to development of appropriate, gender-specific reference standards are the confounding influence of cardiovascular disease, particularly in older adults, or the assumption that data derived from apparently healthy young volunteers can be extrapolated to older adult populations with known or suspected disease. The FHS Offspring cohort consists of middle-aged and older men and women who have undergone periodic medical examinations for more than 25 years. Thus, the study sample is a uniquely well-characterized cohort, from which a healthy, population-based reference sample allows for determination of gender-specific normative CMR reference values.

Gender differences and impact of adjustment for height and BSA. As has been described for both echocardiographic and smaller CMR series, absolute LV mass, EDV, ESV and linear dimensions were significantly greater in men than in women. This emphasizes the need for gender-specific reference values, as use of gender-indifferent threshold values for LV hypertrophy or chamber dilation would lead to reduced sensitivity for women and reduced specificity for men. Data from the present study, as well as previous work by others and us, indicate that LV mass, volume and linear dimensions are significantly correlated with body habitus, so that adjustment is warranted to account for differences in body size (8,9,18,19). As in these prior reports, we reported adjustment with respect to body height and to BSA; these measures are commonly used to index cardiac data with other imaging modalities. Height is simple to determine and is strongly associated with lean body mass (19), may best reflect metabolic demands on the heart (20), and does not make allowance for obesity. Direct measurement of lean body mass is difficult to acquire in the clinical setting. Obesity is associated with LV hypertrophy (21,22); indexing LV measurements by weight thus might fail to detect pathologic levels of LV mass and, accordingly, was not developed in this report. Body surface area makes partial allowance for obesity, as weight is used in conjunction with height to determine BSA. In the present study, gender differences persisted after adjustment for height, except in the case of EDD, which was similar in men and women. Adjustment for BSA resulted in a tendency toward "crossover" with greater linear dimensions in women compared with men. The physiologic or prognostic implications of this gender-differential effect of adjustment for BSA are unknown and await further study with a larger cohort.

Comparison with previous CMR studies. Several investigators have reported normal CMR indexes for cardiac anatomy and function based on findings from relatively young cohorts. In the two largest series to date, Lorenz et al. (8) reported normal LV CMR values in 75 healthy subjects (28 women, 47 men; age 28 ± 9 years), and Marcus et al. (9) described LV parameters in 61 healthy young adults (32 men, 29 women; mean age 22 ± 2 years). Consistent with the findings of the present study, both investigators reported greater LV volume and mass in men, before and after adjustment for height and BSA. Compared with our results, however, both Lorenz and Marcus reported greater EDV values, regardless of gender or adjustment method. This may be due in part to the younger age of their participants, or population differences in habitual physical activity. With respect to LV mass, mean values in the Marcus study were lower than corresponding values in our study. This may reflect differences in body habitus, as well as age; the greatest proportional difference was observed after adjustment for height, which does not make allowance for obesity or overweight. Subjects in the Marcus study were substantially taller (men: 1.83 ± 0.07 m, women: 1.71 ± 0.07 m) and leaner (men: body mass index [BMI] = 23.1 ± 2.7 kg/m^2; women: BMI = 21.6 ± 2.5 kg/m^2) than participants in our study (Table 1). The above studies should be viewed as complementary to the present study, as the subjects were principally drawn from a young-adult age group not represented in this report.

Comparison with echocardiographic studies. Although two-dimensional (2D) and three-dimensional (3D) echocardiography are available for measurement of LV anatomy and systolic function, M-mode echocardiography, because of its ease of acquisition and measurement, remains the most widely used method for determination of LV dimension and mass, both in clinical practice and in many research studies. Cardiovascular magnetic resonance imaging-derived LV EDD and wall thickness in the present study were similar to corresponding M-mode derived values obtained from 914 clinically healthy FHS subjects in a separate study (23). In the present study, however, gender-specific values for normal CMR LV mass are lower than previously reported M-mode-derived values obtained from 864 healthy adults drawn from the same FHS Offspring cohort (24) and likely reflect differences between CMR and M-mode echocardiographic derived volumes and mass. In support of this hypothesis, another study of 111 healthy, normotensive adults (25) found that M-mode echocardiographically derived mass was greater than volumetric CMR mass. In a third series of healthy normotensive subjects (19), M-mode values for LV mass are more comparable to our data, although mean M-mode mass still exceeded the CMR mass values of the present study. Notably, the proposed upper 95th percentile "limits of normal" for LV mass in each of the echocardiographic studies (men: 259 g, 143 g/m, 261 g; women: 166 g, 123 g/m, 191 g, respectively, for the three studies) are substantially greater than the corresponding upper 95th percentile values in the present CMR study (Table 2). Although not widely available, 3D echocardiography yields excellent agreement with CMR imaging for LV volume (16) and mass. Analogous to our findings, M-mode derived mass is significantly greater than 3D echo mass in the same subjects (26).

Rationale for CMR imaging. Cardiovascular magnetic resonance imaging is highly reproducible (16,27) and may be particularly advantageous in traditionally difficult-to-image patients with obese body habitus or pulmonary disease, as CMR is not dependent on adequate acoustic windows for imaging (28) and does not suffer from attenuation artifacts associated with radionuclide imaging. In the present study, adequate or better quality images suitable for analysis were obtained in 137 (96.5%) of 142 subjects. Use of recently developed non-breath-hold real-time CMR techniques (29,30) may have allowed acquisition of analyzable images in the remaining five subjects, but we did not pursue this option, in the interest of methodological consistency. In the context of clinical studies, use of CMR imaging may minimize selection bias associated with echocardiography (31), which disproportionally excludes obese and elderly subjects (10). Furthermore, the excellent reproducibility of CMR may allow dramatic reductions in sample size needed to observe response to experimental treatments (7,27).

Study limitations. This study was not designed or powered to address possible age-related changes in LV parameters. However, the FHS study sample represents a clinically relevant adult population, about which CMR normative data were previously unknown. This closely followed cohort allowed us to more carefully screen for hypertension and other potential confounders. The FHS sample was overwhelmingly caucasian. The results of the present study may not be generalized to non-caucasian populations. Finally, we did not control for physical activity, which is known to increase both EDV and LV mass, although such changes are generally considered "physiologic" and are not believed to be indicative of disease (32).

Conclusions. Cardiovascular magnetic resonance imaging determined that LV volume, mass and linear dimensions in a normal adult population free of clinically overt cardiovascular disease are affected by gender and body size. Left ventricular EDV, ESV and mass are all greater in men than in women, regardless of adjustment for height or BSA. This study provides gender-specific CMR reference values for a clinically relevant population in whom cardiovascular disease and hypertension were rigorously excluded, and may serve as normative reference data for this population.

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