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CMR Reference Values for Left Ventricular Volumes, Mass and Ejection Fraction Using Computer-Aided Analysis: The Framingham Heart Study

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Abstract

Purpose—To determine sex-specific reference values for left ventricular (LV) volumes, mass and ejection fraction (EF) in healthy adults using computer-aided analysis and to examine the effect of age on LV parameters.

Methods and Methods—We examined data from 1494 members of the Framingham Heart Study Offspring cohort, obtained using short-axis stack cine SSFP CMR, identified a healthy reference group (without cardiovascular disease, hypertension, or LV wall motion abnormality) and determined sex-specific upper 95th percentile thresholds for LV volumes and mass, and lower 5th percentile thresholds for EF using computer-assisted border detection. In secondary analyses we stratified participants by age-decade and tested for linear trend across age groups.

Results—The reference group comprised 685 adults (423F; 61±9 years). Men had greater LV volumes and mass, before and after indexation to common measures of body size (all $p<0.001$). Women had greater EF (73±6 vs. 71±6%, $p=0.0002$). LV volumes decreased with greater age in both sexes, even after indexation. Indexed LV mass did not vary with age. LV EF and concentricity increased with greater age in both sexes.

Conclusion—We present CMR-derived LV reference values. There are significant age and sex differences in LV volumes, EF and geometry, while mass differs between sexes but not age groups.

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Keywords

left ventricle; reference values; automated border detection; magnetic resonance imaging; epidemiology; aging

INTRODUCTION

Cardiovascular magnetic resonance (CMR) provides accurate and reproducible measures of left ventricular (LV) volumes, mass and ejection fraction (EF) (1,2), but manual delineation of endocardial and epicardial borders is time-consuming and can limit clinical and research throughput. Computer-aided methods for border detection (3–12) are of interest as they offer the potential for time savings and may reduce the level of expertise needed for analysis. A previous study used a computer-aided analysis system, consisting of an automatic border detection (ABD) method with semi-automated tools for manual contour correction if needed, to 1555 LV short-axis CMR data sets from the Framingham Heart Study to assess analysis times and the impact of operator correction of ABD-derived contours (which was minimal) with respect to global parameters of LV volumes, mass and EF (13). The purpose of the present study was to determine sex-specific reference values for LV end-diastolic, end-systolic and stroke volumes (EDV, ESV and SV respectively), mass and EF from a healthy subset of the Framingham Heart Study Offspring cohort using computer-aided analysis. We also sought to assess the effect of age on LV parameters in men and women. The Offspring represent community-dwelling adults of clinically relevant age drawn from a large, community-based, longitudinally followed cohort.

MATERIALS AND METHODS

Study Sample

The Framingham Heart Study Offspring cohort has been previously described (14, 15). Briefly, Offspring are the children of, or spouses of the children of, the original Framingham cohort. The Offspring cohort was initiated in 1971 and its members undergo periodic examinations, or “cycle” visits, every 3–4 years including comprehensive interim history, physical examination, blood pressure measured twice by a physician according to a standard protocol, and morning blood draw after 12-hour overnight fast for laboratory testing, as well as other testing on a cycle-specific basis. Offspring were eligible for CMR if they participated in the cycle 7 visit (1998–2001), were without contraindication to CMR (e.g., pacemaker, cardioverter/defibrillator), or severe claustrophobia; and lived in Massachusetts or a contiguous state. Of the 3539 Offspring who attended cycle 7, 1810 underwent CMR during 2002–2006. All participants provided written informed consent after explanation of the study and associated procedures. The study protocol was approved by the appropriate local Institutional Review Boards.

CMR Imaging

Participants were scanned supine in a 1.5-T system (Gyroscan NT, Philips Healthcare, Best, the Netherlands) using a 5-element cardiac array coil for radiofrequency signal reception. After scout imaging the left ventricle was imaged in the LV short-axis orientation using a steady-state free precession (SSFP) sequence with repetition time = 3.2 ms, echo time = 1.6 ms, 60° flip angle, 208 × 256 matrix with 400-mm field-of-view. Slice thickness was 10 mm with zero interslice gap. Temporal resolution was 30–40 ms.

Image Analysis

A single operator with >12 years and >4000-case experience in manual CMR analyses (C.J.S.) analyzed LV short-axis image data using a commercially available analysis platform with ABD facilities (Extended MR Workspace 2009, Philips Healthcare) (13). Briefly, the operator identified the slice range (base to apex) suitable for ABD, but was not otherwise required to identify the LV blood pool, myocardium or any other image feature. The most basal extent for ABD was selected as the slice in which a complete ring of myocardium was present at end-systole. After ABD, the operator had the option to manually correct contours using a semi-automated tool which could propagate corrections across cardiac phases. Finally, the operator manually delineated any basal LV contours at end-diastole that were not within the initial operator-specified slice-range. Trabeculations and papillary muscles were included in LV cavity volume. After operator approval of the contours, LV EDV, ESV and SV were automatically determined by Simpson's rule and LV mass was determined using a Riemann sum. The LV SV and EF were computed in the usual way, and concentricity was defined as LV mass divided by EDV.

Statistical Analysis

Continuous data are summarized by mean and standard deviation. Differences between sexes were assessed using a 2-sample t test. For purposes of identifying a healthy reference subset, we excluded participants with prior myocardial infarction, heart failure, CMR wall motion abnormality, or any history of hypertension (systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or on antihypertensive medication) since the first Offspring cycle examination. Sex-specific 95th percentiles for LV volumes and mass and sex-specific 5th percentiles of LV EF were prospectively selected as high and low cutpoints, respectively. LV volumes and mass were indexed to standard quantities including height (HT), an allometric power of height (HT$^{2.7}$) and body surface area (BSA). In a pre-specified secondary analysis we performed similar analyses by age group, for participants aged <50 years, 50–59, 60–69 and ≥ 70 years and tested for linear trend across age groups. We considered these secondary analyses due to the relatively low (<100) numbers of participants in the youngest and oldest age groups. Operator reproducibility was assessed in 48 participants, randomly drawn from equal strata of sex and age-decade, using intraclass correlation coefficient (ICC). The second operator (M.L.C.) had >17 years CMR experience. All statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

A total of 1494 LV datasets from the Framingham Offspring cohort were analyzed using the ABD software over a prespecified 6-month analysis period. Of these, 809 were excluded due to prior myocardial infarction or heart failure (n=53), resting wall motion abnormality or depressed EF (<55%, n=125), or hypertension on at least one cycle visit (n=785). Some participants had more than one exclusion criterion. The remaining 685 participants (262 men, 423 women) constituted the reference group, whose baseline characteristics are shown in Table 1.

LV EDV, ESV, SV, mass, EF and concentricity are presented for men and women in Table 2. Men had greater LV volumes and mass than women (all $p<0.0001$), and those differences remained significant after indexation (all $p<0.002$). LV EF was greater in women than men (73±6 vs. 71±6%, $p=0.0002$). LV concentricity, as measured by LV mass to EDV ratio, was greater in men than women. For purposes of identifying high volumes, mass and concentricity the sex-specific 95th percentiles are shown in Table 2. For low EF, sex-specific 5th percentiles are shown.

LV volumes and mass determined by computer-aided analysis were highly reproducible, with intraobserver ICCs for EDV, ESV, SV and LV mass of 0.99, 0.98, 0.99 and 0.99, respectively. Intraobserver ICC for EF was 0.98. Similarly, interobserver ICCs were 0.99, 0.98, 0.99, 0.99 and 0.96, respectively, for EDV, ESV, SV, LV mass, and EF.

Examination of LV parameters by age group (Table 3) showed that both EDV and ESV decreased significantly with greater age in both sexes (p-value for linear trend $p<0.0001$). These negative linear trends remained statistically significant after indexation to HT, $HT^{2.7}$ and BSA. There was no significant linear trend between increasing age-group and LV mass in men. Unindexed LV mass decreased significantly with increasing age-group in women, but this trend was no longer statistically significant after indexation to HT, $HT^{2.7}$ and BSA. LV EF increased with increasing age group ($p <0.0001$) among men and among women. LV concentricity increased with increasing age-group in both sexes; a relationship driven primarily by decreasing EDV.

DISCUSSION

In this study we used computer-aided analysis for automated detection of LV epicardial and endocardial borders to determine reference values for LV volumes, mass and EF from cine SSFP images in a longitudinally followed cohort of community dwelling adults free of clinical cardiovascular disease and hypertension. Consistent with prior reports using fully manual analyses (16–19), we found that men had greater LV volumes and mass than women, with preservation of these sex-differences after indexation to height and body surface area. Also consistent with these prior studies, women had significantly greater EF than men (20). In secondary analyses relating age-decade groups to LV parameters, we noted significant decreases in LV volumes with increasing age, but no linear trend in indexed LV mass across age groups. LV EF increased with greater age in both sexes. As might be expected with use of ABD, both inter- and intraobserver reproducibility were very high.

A wide variety of methods have been applied to the challenging problem of automated or semi-automated border detection in CMR images. Although short-axis cine SSFP images, as in the present study, are probably more amenable to automated endocardial border definition as compared with older segmented k-space gradient-echo sequences (due to superior conspicuity of the endocardium-blood pool interface), endocardial ABD is still difficult due to the presence of trabeculations and papillary muscles. The current ABD algorithm seems to provide endocardial borders very close to fully manual contours using methods previously described (13,21), which proceed from a ring-detection method to identify the short-axis LV, followed by modeling the LV as a ribbon-like structure of variable width using energy minimizing criteria to favor smooth circular shapes segmentally most consistent with local edge and ridge features.

Prior studies of ABD-assisted LV analysis have demonstrated feasibility and/or accuracy of automated border detection, but most employed relatively small numbers of subjects and did not have longitudinal data on factors that could affect LV structure and function. This report presents our experience using a commercially available analysis package on a sizeable cohort of adults in the context of an on-going epidemiological study and is one of the largest study samples to which ABD methods have been applied. The well-characterized nature of the FHS Offspring cohort allowed us to identify participants with major risk factors for LV hypertrophy, including any history of hypertension, and those with clinical CVD. Exclusion of these participants from the reference subgroup enabled us to determine sex-specific normative values for LV volumes, mass and EF by CMR.

Our finding of decreased LV volumes with increasing age, even after indexation to body size measures, is consistent with prior reports (17,18,22). The underlying mechanism may be in part related to decreased physical activity with greater age, but we did not control for physical activity. In contrast with some prior findings (18), we did not detect a linear trend of decreasing LV mass with greater age. This may be due to small (from an epidemiologcal perspective) sample sizes in the youngest and oldest age groups, or remodeling associated with factors not accounted for in our study. Alternatively, the difference may also be related to the low number of patients per age group in the prior study (18). Our results regarding age and LV mass were consistent with results from the Multiethnic Study of Atherosclerosis (MESA), which similarly failed to find a decreased in indexed LV mass with greater age (17). Quantitative results from the MESA study, which used a fast gradient-echo imaging sequence, are not directly comparable to our results which are SSFP-based, as there is a systematically greater LV volume and lower mass with SSFP. However, it is reassuring that sex and age were similarly associated, or not as the case may be, with LV volumes and mass in both the MESA and the present study. Although we present age-group means for LV volumes, mass and EF, we do not present age-group specific reference limits due to sample size concerns. In general, reference values should be determined from “bin sizes” of at least 120 samples for confidence in 95th percentile limits (120 if normally distributed, and at least 200 samples for non-Gaussian measures (23)).

The principal contributions of this study are twofold. First, we studied a relatively large group of community-dwelling adults from the established and well-characterized Framingham Heart Study Offspring cohort, thus avoiding the pitfall of referral bias, as can exist in studies of “healthy volunteers” recruited *ad hoc* from amongst co-workers or the like, and meticulously identified a reference subgroup free of hypertension (over decades prior to and up through CMR scanning) and clinical cardiovascular disease including heart failure and myocardial infarction, resulting a reference sample large enough to generate upper 95th and lower 5th percentile thresholds with confidence. Second, we present reference values appropriate for the computer-assisted analysis protocol; the computer-aided analysis protocol defines the end-systolic LV base as a plane, whereas our manual analysis protocol allows tracing an additional “partial slice” at end-systole if desired (as is the case for end-diastole in both the fully manual and computer-assisted protocols).

Manual analysis of LV volume, mass and EF can be time consuming and is dependent on operator experience to produce accurate results. ABD offers the potential to decrease analysis times. Although it is possible for an experienced operator to determine EDV, ESV, mass and EF manually in less than 10 minutes, of necessity endocardial contours are traced at only two cardiac phases, while epicardial contours are generally only traced at diastole. Determination of LV contours across cardiac phases offers the possibility of generating filling curves, or assessing regional wall thickening in addition to wall thickness, and these remain to be investigated in the Offspring cohort.

Interobserver reproducibility was high in this study, as might be expected from two operators with extensive experience in analysis of CMR data. Despite the use of ABD, results were not identical due to the possibility for manual adjustment of contours, and more importantly, due to the need for operators to identify and delineate the LV base at end-diastole. Whether novice operators, with minimal CMR experience, can achieve results more congruent with those of experts by using the ABD software (as compared with novice-performed versus expert-performed manual analyses) remains to be determined. If so, use of such computer-assisted analysis methods may improve not only single time-point accuracy, but may facilitate comparison of serial examinations, particularly with different operators at the different time points.

The Offspring cohort is largely white and middle-aged or older. Whether the normative values presented here generalize to other age groups or races/ethnicities is unknown. Possible ethnic differences in LV volumes and mass were investigated in the MESA cohort (17), but could not be addressed in the present study. Additionally, the Offspring cohort is largely sedentary. Greater LV volumes and mass may be expected in more physically active adults of similar age, particularly endurance athletes (24), and the clinician must of course take such factors into account before labeling a given patient as having pathologically increased LV volume or mass.

In conclusion, we presented sex-specific reference values for LV EDV, ESV, SV, mass and EF, in a cohort of longitudinally followed adults of clinically relevant age strictly free of cardiovascular disease and hypertension, using computer-assisted analysis. The software automatically identified the left ventricle in over 99% of contours, with minimal need for operator correction of automatically-detected contours. Such methods may be suitable for inclusion in busy clinical workflows or large research studies.

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Table 1

Baseline characteristics of the healthy reference group (mean±SD).

	Men	Women	P, Men vs. Women
N	262 (38.2%)	423 (61.8%)	
Age, years	60.7±8.5	61.7±8.6	<0.0001
Height, m	1.76±0.07	1.62±0.06	<0.0001
Weight, kg	84.6±11.8	67.9±12.4	<0.0001
Body mass index, kg/m^2	27.2±3.5	25.8±4.4	<0.0001
Body surface area, m^2	2.03±0.16	1.74±0.17	<0.0001
Systolic blood pressure, mmHg	117±10	114±12	0.0001
Diastolic blood pressure, mmHg	73±7	70±8	<0.0001

Table 2

Left ventricular volumes, mass and ejection fraction by sex in the healthy reference group.

	Men		Women		
	Mean±SD	**P95**	**Mean±SD**	**P95**	**P, Men vs. Women**
Unindexed					
EDV, ml	149±29	**197**	112±21	**149**	<0.0001
ESV, ml	44±14	**69**	31±9	**47**	<0.0001
SV, ml	105±20	**139**	81±15	**105**	<0.0001
LVM, g	99±21	**133**	58±13	**80**	<0.0001
LVM/EDV	0.85±0.15	**1.15**	0.74±0.11	**0.95**	<0.0001
Indexed for HT					
EDV/HT	85±16	**111**	69±12	**87**	<0.0001
ESV/HT	25±8	**39**	19±5	**28**	<0.0001
SV/HT	60±11	**78**	50±9	**64**	<0.0001
LVM/HT	56±11	**74**	36±7	**49**	<0.0001
Indexed for $HT^{2.7}$					
$EDV/HT^{2.7}$	32±6	**43**	30±5	**38**	<0.0001
$ESV//HT^{2.7}$	10±3	**15**	8±2	**12**	<0.0001
$SV//HT^{2.7}$	23±4	**30**	22±4	**28**	0.002
$LVM//HT^{2.7}$	21±5	**29**	16±3	**22**	<0.0001
Indexed for BSA					
EDV/BSA	74±14	**99**	64±10	**80**	<0.0001
ESV/BSA	22±7	**34**	18±5	**26**	<0.0001
SV/BSA	52±9	**67**	46±7	**59**	<0.0001
LVM/BSA	49±9	**64**	33±6	**44**	<0.0001
	Mean	**P5**	Mean	**P5**	
LV EF, %	71±6	**60**	73±6	**63**	0.0002

P95 indicates the upper 95th percentile limit; P5 the 5th percentile limit. BSA=body surface area, EDV=end-diastolic volume, EF=ejection fraction, ESV=end-systolic volume, HT=height, LVM=left ventricular mass, SV=stroke volume. Concentricity is denoted by LVM/EDV.

Table 3

Left ventricular parameters by sex and age-decade.

Age Group	<50 years	50 – 59 y	60 – 69 y	≥70 y	P value
MEN	N=26	N=104	N=94	N=38	
Unindexed					
EDV, ml	161±28	155±27	145±29	136±28	<0.0001
ESV, ml	53±16	47±13	41±14	37±10	<0.0001
SV, ml	109±18	109±19	103±20	99±21	0.005
LVM, g	94±13	103±20	96±22	97±20	0.36
LVM/EDV	0.77±0.12	0.84±0.17	0.85±0.16	0.92±0.30	0.0036
LV EF, %	68±6	70±6	72±6	73±5	<0.0001
Indexed for HT					
EDV/HT	91±15	88±15	82±16	78±16	<0.0001
ESV/HT	30±9	26±7	24±8	21±6	<0.0001
SV/HT	62±10	61±10	59±11	57±12	0.016
LVM/HT	53±7	58±11	55±12	56±12	0.62
Indexed for $HT^{2.7}$					
EDV//$HT^{2.7}$	35±6	33±6	32±6	30±6	0.0009
ESV//$HT^{2.7}$	11±3	10±3	9±3	8±2	<0.0001
SV//$HT^{2.7}$	24±4	23±4	23±4	22±5	0.12
LVM//$HT^{2.7}$	20±3	22±5	21±5	22±5	0.80
Indexed for BSA					
EDV/BSA	79±12	76±13	71±14	69±14	0.0001
ESV/BSA	26±7	23±6	21±7	19±5	<0.0001
SV/BSA	54±9	53±9	51±9	50±11	0.03
LVM/BSA	46±5	50±9	47±9	49±9	0.73
WOMEN	N=24	N=179	N=139	N=81	
Unindexed					
EDV, ml	127±22	116±21	108±19	103±17	<0.0001
ESV, ml	38±10	33±9	30±9	25±7	<0.0001

Age Group	<50 years	50 – 59 y	60 – 69 y	≥70 y	P value
SV, ml	89±17	83±16	78±13	78±13	<0.0001
LVM, g	68±18	59±13	56±11	58±11	0.009
LVM/EDV	0.70±0.09	0.72±0.86	0.74±0.11	0.78±0.12	<0.0001
LV EF, %	70±6	71±6	73±5	76±5	<0.0001
Indexed for HT					
EDV/HT	77±12	71±12	67±11	64±10	<0.0001
ESV/HT	23±6	20±5	18±5	16±4	<0.0001
SV/HT	54±10	51±9	49±8	49±8	0.002
LVM/HT	41±10	36±8	35±6	36±7	0.065
Indexed for $HT^{2.7}$					
$EDV//HT^{2.7}$	33±5	31±5	30±5	29±5	<0.0001
$ESV//HT^{2.7}$	10±2	9±2	8±2	7±2	<0.0001
$SV//HT^{2.7}$	23±5	22±4	22±4	22±4	0.18
$LVM//HT^{2.7}$	17±4	16±3	15±3	16±3	0.79
Indexed for BSA					
EDV/BSA	69±8	66±10	62±9	61±9	<0.0001
ESV/BSA	21±5	19±5	17±5	15±4	<0.0001
SV/BSA	48±6	47±8	45±7	46±7	0.02
LVM/BSA	37±7	34±6	33±5	34±6	0.27

P-value for linear trend across age groups. BSA=body surface area, EDV=end-diastolic volume, EF=ejection fraction, ESV=end-systolic volume, HT=height, LVM=left ventricular mass, SV=stroke volume. Concentricity is denoted by LVM/EDV.