Published in final edited form as:

J Magn Reson Imaging. 2015 April ; 41(4): 1038–1045. doi:10.1002/jmri.24649.

Impact of Age, Sex and Indexation Method on MR Left Ventricular Reference Values in the Framingham Heart Study Offspring Cohort

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Abstract

Purpose—To determine normative values for left ventricular (LV) volumes, mass, concentricity and ejection fraction (EF) and investigate associations between sex, age and body size with LV parameters in community dwelling adults.

Materials and Methods—1794 Framingham Heart Study Offspring cohort members underwent LV short-axis oriented, contiguous multislice ciné SSFP MR of the left ventricle; from these a healthy referent group (N=852, 61±9 years, 40% men) free of clinical cardiac disease and hypertension (SBP<140, DBP<90 mmHg, never used antihypertensive medication ≥ 30 years prior to scanning) was identified. Referent participants were stratified by sex and age group (≤55, 56-65, >65 years); LV parameters were indexed to measures of body size.

Results—Men have greater LV volumes and mass than women both before and after indexation to height, powers of height, and body surface area ($p<0.01$ all), but indexation to fat-free mass yielded greater LV volume and mass in *women*. In both sexes, LV volumes and mass decrease with advancing age, though indexation attenuates this association. LVEF is greater in women than men (68±5% vs. 66±5%, $p<0.01$) and increases with age in both sexes ($p<0.05$).

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Conclusion—Among non-hypertensive adults free of cardiac disease, men have greater LV volumes and mass with sex differences generally persisting after indexation to body size. LV volumes and mass tend to decrease with greater age in both sexes. Female sex and advanced age were both associated with greater LVEF.

Keywords

magnetic resonance imaging; left ventricle; aging; sex differences; population study; reference values

INTRODUCTION

Normative reference values for left ventricular (LV) parameters such as volume, mass or wall thickness are useful for classification of patients and identification of pathology. Magnetic resonance using modern steady state free precession (SSFP) cine imaging provides excellent endocardial border definition and allows use of standardized cardiac imaging planes independent of acoustic windows and cardiac orientation (1). Volumetric MR assessments of ventricular mass, volume and systolic function are highly reproducible (2,3). In research studies across multiple subjects this allows detection of changes in structural parameters with smaller sample sizes than needed for M-mode or 2D echocardiography (1,2). For the individual patient, the high reproducibility of MR allows identification of smaller changes between serial examinations than is typically possible with echocardiography. Thus it is important to have SSFP MR-based LV reference values drawn from an appropriate population, taking into account body size (via indexation) as well as possible differences between the sexes and across age groups.

Prior estimates of the relationships between body size, age and sex to LV anatomy and function mostly have been based upon relatively small sample sizes in the presence of potential confounders (e.g. including individuals with hypertension, a history of hypertension, or “self reported” healthy) or have used older gradient-recalled echo (GRE) cine MR, sequences (4-10). Further, few studies have reported results indexed to fat-free mass (FFM), which some have advocated as an indexation variable on the basis that FFM is a superior estimate of metabolic demand (11).

MATERIALS AND METHODS

Members of the Framingham Heart Study (FHS) Offspring Cohort who participated in the cycle 7 examination (1998-2001) were eligible for MR study (12). Briefly, the Offspring comprise the children of the original FHS cohort as well as the spouses of those children. FHS Offspring cohort members have undergone serial comprehensive examinations and interval history every 3-4 years since the first Offspring cycle exam (1971-1975). At each cycle exam, the mean of two physician-acquired blood pressures, using a mercury sphygmomanometer, is determined. Offspring were prospectively excluded from MR scan recruitment if they had contraindications to MR (e.g., intracranial or intraocular metal; pacemaker, defibrillator or other implanted electronic device; severe claustrophobia), if they were in non-sinus rhythm, or if they did not live in Massachusetts (site of MR scanning) or a contiguous state.

A total of 1794 Offspring underwent MR during 2002-2006. For purposes of generating normative values, we prospectively excluded from this analysis any participant who had a history of hypertension (systolic blood pressure (SBP)≥140mmHg, diastolic blood pressure (DBP)≥90mmHg) or had received any antihypertensive medication at any cycle visit). The hypertension criterion excluded 904 of the 1794 Offspring. Study participants were also excluded if they had a resting MR wall motion abnormality, determined visually by a cardiologist with level 3 cardiac MR training, S.B.Y. or W.J.M., n=33 (13), or any history of myocardial infarction or heart failure (n=5). The final sample comprised 852 Offspring cohort members.

The study was approved by the appropriate local institutional review boards. All participants gave written informed consent.

MR Imaging

MR imaging was performed with participants supine in a 1.5-T MR scanner (Gyroscan NT, Philips Medical Systems, Best, The Netherlands), with a commercial 5-element cardiac array receiver coil. Following localizing scans, 2D end-expiratory breath-hold, ECG-gated SSFP cine images were obtained in the LV short-axis orientation encompassing the LV from base to apex (repetition time=R-R interval, TR=3.2ms, TE=1.6ms, flip angle 60 degrees, field-of-view 400mm, matrix size 208×256, slice thickness 10mm, interslice gap=0, temporal resolution 30-40ms). A single slice was acquired with each 10-15 second breath-hold.

Fat-Free Mass Measurement

FFM was measured by dual x-ray absorptiometry (DXA) with a Lunar DPX-L bone densitometer (Lunar Corp., Madison, WI) (14,15) during the Offspring cycle 6 examination (1996-2000).

MR Image Analysis

Image analyses were performed using commercial software (EasyVision 5.1, Philips Medical Systems) by a single observer with 8 years of MR experience (C.J.S.) blinded to all clinical data. Single measurements of the LV inferolateral and anteroseptal wall thicknesses (IWT and SWT) and end-diastolic diameter (EDD) were performed at end-diastole, at the slice immediately basal to the tips of the papillary muscles. Quantitative measures of LV cavity size and mass were obtained by manually segmenting LV contours at end-diastole and end-systole. Papillary muscles and trabeculae were included as LV cavity volume.

LV cavity end-diastolic volume (EDV) and end-systolic volume (ESV) were computed using an interpolated summation of discs method. LV ejection fraction (LVEF) was computed as (EDV-ESV)/EDV × 100%. LV mass (LVM) was determined by multiplying the end-diastolic myocardial volume by myocardial density (1.05 g/ml). Relative wall thickness (RWT) was calculated as (IWT + SWT)/EDD and concentricity as LVM/EDV. Segmental LV wall motion was analyzed using standard methods (16).

Volumetric LV parameters were indexed to measures of body size: body surface area (BSA, m^2), height (HT, m), allometric powers of height ($HT^{1.7}$ and $HT^{2.7}$), and FFM (kg). Unidimensional (linear) LV measures were indexed to HT only.

Reproducibility of MR measures were conducted using a randomly selected sub-sample of 48 participants (24 women) stratified across age tertiles. Two expert observers, each blinded to clinical data and the other observer's results, independently conducted the measurements. Reliability was evaluated using intra-class correlation (ICC) (17).

Statistical Analyses

Unindexed and indexed LV data were analyzed separately by sex. Continuous variables are summarized as mean±SD. We also report sex-specific 95^{th} percentile upper limits (or 5^{th} percentile lower limits as appropriate) for purposes of generating normative reference values. Sex differences were assessed using a two-sample t-test. To investigate possible changes with advancing age, we defined three age groups (≤55, 56-65, >65years) and tested for linear trend across the age groups. The age-group cutpoints were selected with the intention of having at least 100 study participants in each age-and-sex "bin" if possible, for statistical robustness. Although we included only normotensive participants in this analysis, there was an increase in SBP with increasing age category among both men and women, thus ANCOVA was used to further adjust linear regression models for SBP. All analyses were performed with SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Of the 1794 Offspring cohort members who underwent MR, 852 (340 men) were free of any history of hypertension and were without prevalent myocardial infarction, heart failure or wall motion abnormality. These participants formed the healthy referent group and their clinical characteristics are shown in Table 1.

Sex-Related Differences

Sex-specific mean, standard deviation and upper 95^{th} percentile (or lower 5^{th} percentile) LV measures are presented in Table 2. LVEF was greater in women than men ($p<0.001$). Raw LV volumes (EDV, ESV, SV) and LVM were greater in men than women ($p<0.0001$ for all). Sex differences persisted after indexation to BSA, HT and powers of HT (Table 3). However, indexation to FFM resulted in greater EDV/FFM and SV/FFM in *women* ($p<0.001$) and negated sex differences in ESV/FFM and LVM/FFM.

Unidimensional LV measures (wall thicknesses and EDD) were lower in women ($p<0.0001$; Table 2. Wall thicknesses indexed to HT remained significantly lower in women ($p<0.0001$) but EDD/HT did not differ between women and men (Table 3).

Both unidimensional (RWT) and volumetric (LVM/EDV) concentricity measures were smaller in women ($p<0.0001$)(Table2).

Associations With Age

Clinical characteristics by sex and age group are presented in Table 4. Although all study participants were normotensive, SBP increased with advancing age group in both sexes ($p<0.0001$); thus age-group analyses were adjusted for SBP. Unindexed LV volumes (EDV, ESV, SV) and LVM *decreased* with greater age in both sexes (p for trend <0.01 for all measures); these trends persisted after indexation (Table 5) to HT, powers of HT, BSA and FFM. With respect to unidimensional measures, EDD decreased with greater age in both sexes with and without indexation to HT ($p<0.05$). Volumetric concentricity (LVM/EDV) increased with greater age group in both sexes ($p<0.01$ men, <0.05 women), while RWT did not show a linear trend with age (Table 4). LVEF increased with greater age group among men ($p=0.05$) and among women ($p<0.0001$).

Reproducibility

Reproducibility was high, with intra-observer ICCs of ≥0.98 for LV volumes and LVM and 0.97 for LVEF. Interobserver ICCs were similar for LV volumes and LVM at ≥ 0.98, but slightly lower at 0.95 for LVEF.

DISCUSSION

In this prospective cross-sectional study of a longitudinally and closely followed population strictly free of clinical cardiovascular disease and hypertension, we provide sex-specific normative values for MR SSFP measures of LV anatomy, with and without indexation to various measures of body size, and for LVEF. As a secondary analysis, we present the association between advancing age and LV parameters.

Overall, our findings that men had greater LV volumes, mass and concentricity (as defined by the LVM/EDV ratio) are consistent with the literature across multiple cardiac imaging modalities (8,9,18-21). The finding of slightly but significantly lower LV EF in men is consistent with a prior report from the Dallas Heart Study, which principally used an older gradient-recalled echo (GRE) sequence (9). However, we found indexing to FFM *reversed* the direction of sex differences in LV volumes; this was unexpected and has not been previously explored. If FFM truly better represents cardiovascular demand than other measures of body size, it may be that women have greater cardiac structural response to demand than men. Alternatively, it may be that DXA underestimates FFM in women as compared with men (22); using a DXA system similar to that in the present study, Roche et al found that DXA underestimated FFM by 1.1 kg in women, versus 0.2 kg in men as compared with a multi-compartment model of body composition.

The magnitude of age-related change for LVM and cavity volumes was relatively small (~10-20%) across the three age groups, but these differences were sufficient to have an impact on normative values. Age-related decreases in LVM are attenuated by indexation to body size but generally remain significant even after adjusting for SBP. Attenuation of age-related linear trends in LVM after indexation to allometric powers of HT or FFM suggests that powers of HT or FFM may serve as markers of age-related metabolic demand.

Our finding of smaller LV cavity volumes with advancing age is consistent with the literature (8,23). Using GRE sequences, investigators from the Multiethnic Study of Atherosclerosis (MESA), also reported that LVEDV and LVEDV/BSA declined with age in both sexes (8). In the MESA study, LVM (but not LVM/BSA) was inversely associated with age in men, but not in women. Although total sample sizes in the MESA report and our study are similar, greater ethnic homogeneity in the largely European-descended FHS Offspring cohort may have provided greater power to detect age-related differences in both sexes. Although sex differences and trends with age are similar between the MESA findings and the present study, quantitative measures cannot be directly compared between GRE-based and SSFP-based results, as SSFP imaging produces *lower* LVM and *greater* chamber volumes when compared with GRE sequences (7); these systematic differences probably stem from the greater dependence on inflow for contrast between the bloodpool and endocardium in GRE-based cine imaging as compared with SSFP-based approaches that are more dependent on T1 and T2 properties rather than inflow. Similar declines in unindexed and indexed LV volume with increasing age have been observed by others using SSFP sequences. Maciera et al showed a decrease in LVEDV and LVEDV/BSA with greater age from the third to eighth decade of life (23), an age range similar to our population. While the study of Maciera et al also included younger participants (those in their 20's), they had much smaller sample sizes, with only 10 study participants in each age-and-sex category.

Unidimensional LV parameters decrease with greater age when indexed to unidimensional body size measures but not when indexed to two- or three-dimensional body size variables (data not shown). Although RWT, a linear measure of LV concentricity, increased with age in an M-mode echocardiographic study by Ganau and colleagues (24), we found increases in MR measures of volumetric (LVM/EDV) but not linear (RWT) concentricity with greater age. A possible explanation for this apparent discrepancy is that the higher temporal and spatial resolution of M-mode echocardiography may provide a more precise measure of RWT. However, LVM/EDV, the volumetric analog of RWT, appears to be a robust MR measure. The observed increase in LVM/EDV with greater age is concordant with MESA results using GRE imaging (25).

We used two-dimensional, single slice per breath-hold SSFP imaging and performed LV analyses manually. Three-dimensional acquisitions or multislice-per-breath-hold methods could have decreased scanning time, and semi-automated border detection methods would have decreased analysis times, but at the time of study inception many such techniques were under development or refinement, so we selected conservative but proven methods. Also, we felt that such methods might be perceived as more widely applicable to clinical practice.

Our study extends the literature in several ways. In contrast to prior studies using older GRE sequences, we used a modern SSFP imaging sequence, so that the sex-specific normative values reported herein are directly applicable to current clinical practice. This report is based on results from 340 men and 512 women, an adequate sample size for determination of sex-specific normative reference values. In general, reference values should be determined from sample sizes of at least 120 individuals per "bin" for normally-distributed quantities, and at least 200 for non-normal measures (26). "Normative value" studies employing smaller bin sizes may lack statistical robustness. Finally, the FHS Offspring study participants have

been closely followed across detailed serial examinations for nearly three decades. This allowed us to strictly exclude not only persons with overt cardiovascular disease, but also persons with subclinical potential confounders such as a history of hypertension or resting wall motion abnormality, which could affect LVM and concentricity.

We compared various indexing methods and examined differences in age-related linear trends and sex differences after indexation. Although indexing to BSA is commonly used, observations from echocardiographic studies using unidimensional measures suggest that BSA may obscure LV hypertrophy associated with obesity (27). Height$^{2.7}$ is an allometric measure of body size that has been advocated as a potentially useful index for volumetric parameters such as LVM (28), with M-mode echocardiographic LV hypertrophy identified by LVM/HT$^{2.7}$ threshold more strongly predictive of incident CV events than LVM/BSA (27,29). Others have advocated FFM as a superior measure for indexation on the basis that it may more accurately reflect metabolic and thus cardiovascular demand (30,31). In the Strong Heart Study FFM correlated more strongly with echocardiographic LVM than height-based surrogates for lean body mass or SBP (32). However, direct FFM measurement is impractical in the clinical setting, and formula-based surrogate estimates of FFM (33) may be more applicable.

Our data do not allow us to identify a preferred method of indexation to account for body size. Ideally, one would apply multiple candidate indexation methods to the same population, adjust for pertinent risk factors, and then determine which indexation method was most predictive of future major adverse cardiovascular disease events. Although our sample sizes are reasonably robust, the length of follow-up and the relatively low number of adverse events preclude such analyses at present.

Our normative data are derived from a community-based population of middle-aged to older adults of European descent and may not be generalizable to other age and ethnic groups. Associations between age and measured LV parameters were cross-sectional and not longitudinal. We did not perform serial MR examinations over the life of each study participant. Age group differences may reflect generational differences rather than changes that would occur in an individual over time (34,35). Finally, observer reproducibility was assessed in only a small subset (N=48) of the overall study sample (N=852).

In conclusion, normative values for LV volumes, mass and EF using a modern cine SSFP sequence are presented based on a closely followed, community-dwelling population strictly free of hypertension and clinical cardiovascular disease. LV volumes and LVM are inversely associated with advancing age, while LVEF increases with advancing age in both men and women. Unindexed LV parameters are smaller in women as compared to men, but the direction of indexed sex-related differences is dependent on the method of indexation. Our findings support indexing to dimensionally consistent measures of body size (36) and demonstrate the importance of sex and age with respect to normative values.

Acknowledgments

We thank Douglas P. Kiel, MD, MPH for the FFM measurements; DXA scanning was funded by a grant from the National Institute of Arthritis Musculoskeletal and Skin Diseases and the National Institute of Aging (R01 AR/AG 41398).

Grant Support : Supported in part by grants R01 AG17509, N01-HC-38038 and N01-HC-025195 from the National Institutes of Health.

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Table 1

Clinical characteristics of the referent group

	Men	Women
N (%)	340 (39.9%)	512 (60.1%)
Age, years	61±8	62±9
Systolic blood pressure, mmHg	118±10	114±12
Diastolic blood pressure, mmHg	74±7	70±8
Height, m	1.76±0.07	1.62±0.06
Weight, kg	85.1±12.0	68.3±13.1
Body surface area, m^2	2.03±0.16	1.75±0.18
Body mass index, kg/ m^2	27.4±3.6	25.9±4.6
Fat-free mass, kg	59.5±6.4	39.1±4.3

Values are mean±standard deviation (SD).

Table 2

Left ventricular size and structure by sex, unindexed values

	Men			Women		
	Mean±SD	**P5**	**P95**	**Mean±SD**	**P5**	**P95**
EDV, ml	144±26*	105	**188**	108±19	82	**142**
ESV, ml	50±13*	28	**74**	35±10	21	**52**
Stroke volume, ml	95±16*	69	**123**	73±12	56	**94**
LVM, g	123±21*	93	**160**	82±15	62	**109**
LVEF, %	65.8±5.3*	**58.6**	75.3	68.0±5.1	**60.6**	77.7
CO, L/min	5.87±1.12*	**4.30**	7.90	4.75±1.00	**3.40**	6.70
Concentricity (LVM/EDV)	0.87±0.16*	0.66	**1.16**	0.77±0.11	0.61	**0.97**
EDD, mm	52.5±4.5*	45.5	**59.7**	48.3±3.7	42.3	**54.0**
SWT, mm	8.3±1.3*	6.4	**10.7**	7.1±1.1	5.6	**9.3**
IWT, mm	7.3±1.1*	5.6	**9.1**	6.1±1.0	4.6	**7.8**
RWT	0.28±0.16*	0.21	**0.38**	0.25±0.05	0.18	**0.34**

*p<0.0001 men vs. women.

SD = standard deviation, P95 = upper 95th percentile, P5 = lower fifth percentile EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; LVM = left ventricular mass; EF = left ventricular ejection fraction; CO = cardiac output; EDD = end-diastolic diameter; SWT = septal wall thickness; IWT = inferolateral wall thickness, RWT = relative wall thickness.

Table 3

Left ventricular size and structure by sex, indexed to measures of body size; 95th percentile upper limits

	Men					Women				
	/HT	/HT$^{1.7}$	/HT$^{2.7}$	/BSA	/FFM	/HT	/HT$^{1.7}$	/HT$^{2.7}$	/BSA	/FFM
EDV	82±14*	55±9*	31±6*	71±12*	2.42±0.40*	66±11	47±7	29±4	62±9	2.72±0.38
ESV	28±7*	19±5*	11±3*	25±7*	0.85±0.21	21±6	15±4	9±2	20±5	0.88±0.21
SV	54±9*	36±6*	20±4†	47±8*	1.56±0.24*	45±7	32±5	20±3	42±6	1.85±0.25
LVM	70±11*	47±8*	27±5*	61±9*	2.03±0.30	50±8	36±6	22±4	47±7	2.07±0.30
CO	3.33±0.60*	2.24±0.40*	1.27±0.23	2.89±0.50*	0.10±0.02*	2.93±0.58	2.08±0.41	1.29±0.26	2.72±0.49	0.12±0.02
EDD	29.8±2.6					29.8±2.2				
SWT	4.7±0.8*					4.4±0.7				
IWT	4.1±0.6*					3.7±0.6				
	Upper 95th percentile limits									
EDV	106	72	42	93	3.08	86	60	37	76	3.40
ESV	42	28	16	36	1.23	32	22	13	28	1.23
SV	68	46	27	60	1.93	56	40	25	52	2.28
LVM	89	61	35	75	2.53	66	47	29	60	2.60
CO	4.38	2.95	1.69	3.73	0.12	4.05	2.85	1.74	3.58	0.16
EDD	34.3					33.2				
SWT	6.1					5.8				
IWT	5.2					4.9				

*p<0.0001 men vs. women.

†p=0.0011 men vs. women.

HT = height (m); BSA = body surface area (m^2); FFM = fat-free mass (kg)

Table 4

Left ventricular and selected clinical characteristics by age group

	Men			Women		
	≤55 years	**56-65 y**	**>65 years**	**≤55 years**	**56-65 y**	**>65 years**
	N=81	**N=157**	**N=102**	**N=104**	**N=257**	**N=151**
SBP, mmHg	115±10	118±9	121±11 †	109±11	114±12	117±12 *
HT, m	1.78±0.07	1.77±0.07	1.74±0.06 #	1.65±0.06	1.62±0.06	1.61±0.06 *
WT, kg	86.6±12.0	85.4±11.9	83.4±12.1	71.5±15.3	68.7±13.2	65.5±10.7 †
FFM, kg	61.9±6.3	59.8±6.4	57.4±6.0 *	40.5±4.6	39.2±4.1	38.2±4.3 *
BMI, kg/m^2	27.4±3.4	27.4±3.5	27.4±3.9	26.2±5.2	26.2±4.76	25.3±3.9
EDV, ml	159±23	143±24	135±26 *	118±20	109±18	99±16 *
ESV, ml	56±12	49±12	46±14 *	40±10	35±9	31±9 *
SV, ml	102±15	94±16	89±15 *	78±13	74±12	69±10 *
LVM, g	128±21	123±21	120±23 #	87±16	82±15	80±13 *
EF, %	64.6±4.3	65.9±5.4	66.2±5.7 §	66.1±4.3	68.0±4.8	69.4±10.5 *
CO, L/min	6.28±1.03	5.88±1.12	5.53±1.10 *	5.01±1.17	4.83±0.98	4.45±0.81 *
LVM/EDV	0.82±0.13	0.87±0.14	0.91±0.19 #	0.74±0.10	0.76±0.11	0.81±0.11 §
EDD, mm	54.3±4.0	52.3±4.2	51.5±4.9 *	49.7±3.9	48.4±3.4	47.2±3.6 *
SWT, mm	8.4±1.2	8.3±1.2	8.3±1.4	7.3±1.1	7.1±1.1	7.2±1.2 §
IWT, mm	7.4±1.1	7.3±1.0	7.2±1.1	6.1±1.1	6.0±1.0	6.1±1.0
RWT	0.27±0.05	0.28±0.05	0.28±0.06	0.25±0.05	0.25±0.05	0.26±0.05

MR measures adjusted for systolic blood pressure. Within-sex linear trend across age groups:

§ indicates p<0.05,

# p<0.01,

† p<0.001,

* p<0.0001.

SBP = systolic blood pressure; HT = height; WT = weight; FFM= fat-free mass; BMI = bpdy mass index.

Table 5

Left ventricular characteristics by age group, indexed to measures of body size

	Men			Women		
	≤55 years	56-65 y	>65 years	≤55 years	56-65 y	>65 years
	N=81	N=157	N=102	N=104	N=257	N=151
EDV/HT	89±13	81±13	77±14 *	72±11	67±10	62±9 *
ESV/HT	32±7	28±7	26±8 *	24±5	22±5	19±5 *
SV/HT	57±8	53±9	51±9 *	47±7	45±7	43±6 *
LVM/HT	72±11	70±11	68±13 †	53±9	50±9	49±8 *
CO/HT	3.51±0.51	3.33±0.60	3.17±0.63 *	3.04±0.69	2.97±0.57	2.77±0.49 *
EDD/HT	30.6±2.5	29.6±2.4	29.6±2.8 §	30.2±2.4	29.9±2.1	29.4±2.3 #
SWT/HT	4.7±0.7	4.7±0.7	4.8±0.8	4.4±0.7	4.4±0.7	4.5±6.3
IWT/HT	4.1±0.6	4.1±0.6	4.1±0.7	3.7±0.7	3.7±0.6	3.8±0.7
EDV/ $HT^{1.7}$	60±9	54±9	52±10 *	50±8	48±7	44±6 *
ESV/ $HT^{1.7}$	21±5	19±4	18±5 *	17±4	15±4	14±4 *
SV/ $HT^{1.7}$	38±5	36±6	35±6 *	33±5	32±5	31±4 *
LVM/ $HT^{1.7}$	48±8	47±7	46±9 #	37±6	36±6	35±5 *
CO/ $HT^{1.7}$	2.35±0.34	2.24±0.39	2.15±0.43 †	2.14±0.48	2.12±0.53	1.99±0.35 *
EDV/ $HT^{2.7}$	34±5	31±5	30±6 *	31±5	29±4	28±4 *
ESV/ $HT^{2.7}$	12±3	11±2	10±3 *	10±2	10±2	9±2 *
SV/ $HT^{2.7}$	22±3	20±3	20±4 †	20±3	20±3	19±3 #
LVM/ $HT^{2.7}$	27.3±4.6	26.6±4.0	26.6±5.1 §	22.5±3.7	22.1±3.7	22.1±3.6 #
CO/ $HT^{2.7}$	1.32±0.21	1.27±0.23	1.24±0.26 #	1.30±0.30	1.31±0.25	1.24±0.23†
EDV/BSA	77±11	70±12	68±12 *	66±8	62±9	58±8 *
ESV/BSA	28±6	24±6	23±7 *	22±4	20±5	18±5 *
SV/BSA	50±7	46±8	45±7 *	43±6	42±6	40±5 *
LVM/BSA	62±9	61±9	59±10 #	48±7	46±7	47±7 #
CO/BSA	3.03±0.43	2.89±0.50	2.77±0.53 †	2.79±0.59	2.75±0.48	2.62±0.41 †

J Magn Reson Imaging. Author manuscript; available in PMC 2016 April 01.

	Men			Women		
	≤55 years N=81	56-65 y N=157	>65 years N=102	≤55 years N=104	56-65 y N=257	>65 years N=151
EDV/FFM	2.62±0.34	2.38±0.38	2.32±0.43 *	2.83±0.36	2.75±0.36	2.61±0.39 *
ESV/ FFM	0.96±0.19	0.83±0.20	0.81±0.23 †	0.96±0.19	0.89±0.20	0.80±0.22 *
SV/ FFM	1.66±0.19	1.55±0.25	1.51±0.25 †	1.88±0.25	1.86±0.23	1.81±0.27 §
LVM/ FFM	2.07±0.30	2.05±0.27	1.98±0.33 §	2.10±0.28	2.05±0.29	2.09±0.32
CO/ FFM	0.101±0.015	0.097±0.016	0.093±0.018#	0.122±0.027	0.121±0.021	0.117±0.020 #

MR measures adjusted for systolic blood pressure. Within-sex linear trend across age groups:

§ indicates p<0.05,

# p<0.01,

† p<0.001,

* p<0.0001.