Left atrial structure in relationship to age, gender, ethnicity and cardiovascular risk factors:

the Multi-Ethnic Study of Atherosclerosis (MESA)

Filip Zemrak, MD, MRCP – Centre for Advanced Cardiovascular Imaging, Queen Mary University of London, Barts Heart Centre, United Kingdom

The left atrium in MESA

Bharath Ambale Venkatesh MD - Cardiology Division, Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland, United States

Gabriella Captur, MD, PhD, MRCP, MSc - Institute of Cardiovascular Science, University College London and The Heart Hospital, United Kingdom

Jonathan Chrispin, MD - Cardiology Division, Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland, United States

Ela Chamera, RDCS - Cardiology Division, Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland, United States

Mohammadali Habibi, MD - Cardiology Division, Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland, United States

Saman Nazarian, MD - Cardiology Division, Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland, United States

Saidi A. Mohiddin, MBChB, MD, MRCP – Centre for Advanced Cardiovascular Imaging, Queen Mary University of London, Barts Heart Centre, United Kingdom

James C. Moon, MBBCh, MRCP, MD – Institute of Cardiovascular Science, University College London and The Heart Hospital, United Kingdom

Steffen E. Petersen, MD, DPhil, MPH, FRCP, FESC, FACC – Centre for Advanced Cardiovascular Imaging, Queen Mary University of London, Barts Heart Centre, United Kingdom

Joao A. C. Lima, MD - Cardiology Division, Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland, United States

David A. Bluemke, MD, PhD –Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, United States

Corresponding author:
David A. Bluemke
Department of Radiology and Imaging Sciences
National Institutes of Health Clinical Center
National Institute of Biomedical Imaging and Engineering
10 Center Dr.
Room 1C355
Bethesda
MD 20892
United States
Phone: +1 301.402.1854
Fax: +1 301.402.1854

Email: bluemked@nih.gov

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ABSTRACT

Background: Left atrial (LA) size is a marker of diastolic function and is associated with atrial fibrillation and cardiovascular outcomes. However, there are no large population studies measuring LA structure. The relationship of demographics and cardiovascular risk factors to LA size is largely unknown. This study aimed to determine associations of LA size with demographic factors, cardiac structure and function, and cardiovascular risk factors.

Methods and results: LA volume indexed to body surface area was measured by cardiovascular magnetic resonance SSFP and FGRE cine long- and short-axis images in 2576 asymptomatic participants of the Multi-Ethnic Study of Atherosclerosis (68.7 years, 53.0% women, white 42.2%, Chinese-American 12.0%, black 24.5% and Hispanic 21.2%) using biplane and short-axis images. The mean LA volume index was 36.5 ± 11.4 ml/m^2 in the entire cohort and 35.5 ± 10.1 ml/m^2 in subjects free of cardiovascular risk factors (n=283). Multivariable analysis included adjustment for demographics, ethnicity, cardiovascular risk factors, serologic studies, socioeconomic status, left ventricular structure and medications. In the adjusted analysis, age ($\beta=0.2$ ml/m^2 per year, $p<0.0001$), male gender ($\beta=-4.2$ ml/m^2, $p<0.0001$), obesity ($\beta=1.3$ ml/m^2, $p<0.01$), end-diastolic volume index ($\beta=0.4$ ml/m^2, $p<0.0001$), Chinese-American ($\beta=-2.6$ ml/m^2, $p<0.0001$) and Hispanic ($\beta=1.1$ ml/m^2, $p<0.05$) ethnicities were associated with LA volume index. Diabetes and smoking were not associated with LA volume index. LA volumes measured by SSFP were 3% larger than by fGRE cine CMR ($p < 0.001$).

Conclusions: Age, gender, ethnicity and left ventricular structural parameters were associated with LA size. Importantly, the study provides reference values of normal LA volume index.

Key words: left atrium, cardiovascular magnetic resonance, Multi-Ethnic study of Atherosclerosis

INTRODUCTION

Left atrial (LA) size is a marker of long term left ventricular (LV) diastolic function and is a reliable indicator of severity and duration of diastolic dysfunction.[1] There is strong evidence that LA enlargement is related to atrial fibrillation and is a predictor of cardiovascular outcomes in various conditions: heart failure[2-4], acute myocardial infarction[5-8], cardiomyopathy[9,10] and mitral regurgitation[11] and it has been shown to strongly predict stroke and death.[12,13]

Cardiovascular magnetic resonance (CMR) has an established role in measurement of left and right ventricular volumes, systolic function and mass, with standardized methods of short axis multi-slice acquisition. CMR, due to its accuracy and reproducibility is a reference technique for measurement of ventricular volumes and function, for which reference ranges have been established for the balanced Steady State Free Precession (SSFP) technique.[14,15] LA normal values for SSFP have been published in relatively small healthy volunteer studies by Maceira et al.[14] (120 subjects) and Hudsmith et al.[15] (108 subjects).[16] However, there are no large population based studies using CMR and no data is available that allows an understanding of demographics and cardiovascular risk factors in relationship to atrial dimensions.

SSFP results in larger volumes and lower ejection fraction for the LV compared to fast gradient echo (fGRE) imaging.[17] Comparisons of SSFP versus fGRE for the left atrium (LA) have not been previously available.

The aim of this study was to determine associations of LA volume with demographic factors, cardiac structure and function and with cardiovascular risk factors. We also sought to establish reference values in healthy participants for LA volume using SSFP and fGRE CMR methods.

1

MATERIALS AND METHODS

Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based study of individuals from four ethnic groups free of cardiovascular disease at baseline (2000-2002, Exam 1). At exam 1, 5004 study participants underwent CMR fGRE cine imaging.[18] Of these, 3016 participants underwent CMR imaging between 2010 and 2011 (exam 5) using SSFP cine imaging. However, 498 randomly chosen participants underwent fGRE CMR in addition to SSFP cine acquisitions to allow for standardization between the two techniques. Of those that underwent CMR imaging at exam 5, 416 participants were excluded due to insufficient left atrial image quality and 24 had incomplete cardiovascular risk factor data, respectively, leaving 2576 participants.

Clinical data, including the incidence of atrial fibrillation, myocardial infarction and coronary heart disease were available for all participants. MESA criteria for clinical data (including definitions of hypertension and diabetes) and follow-up procedures have been previously described.[19] Incident AF events were based on MESA-ascertained hospital-discharge International Classification of Diseases - Ninth Revision codes (427.31) and Centers for Medicare and Medicaid Services inpatient hospital claims. Institutional Review Boards of each of the 6 participating field sites in the United States approved the study, and all participants provided written informed consent at the time of enrollment into MESA.

To determine normal LA dimensions we selected a group of participants with normal body mass index (BMI ≥18.5 and < 25 kg/m^2), without hypertension, diabetes, coronary heart disease, heart failure, LV systolic dysfunction (defined as ejection fraction less than 50%), LV hypertrophy or atrial fibrillation (n=283).

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Magnetic resonance imaging

CMR examinations were performed at 6 centers (in Baltimore, Winston-Salem, New York, Minneapolis, Los Angeles, Chicago) using either a Signa Excite (General Electric Medical Systems, Waukesha, WI) or an Avanto/Espree (Siemens, Erlangen, Germany) 1.5-Tesla MR scanners for exams 1 and 5. Planning of the cardiac cine images for both exams was standardized in order to minimize variation between centers. Cine images were obtained with a temporal resolution of 40 milliseconds or less using segmented k-space, retrospectively electrocardiogram-gated long- and short-axis cine images acquired using a SSFP sequence at MESA exam 5 as previously described.[20] Participants (n=362) from Wake Forest University, Winston Salem additionally acquired short axis (SAX) stack cine images of the atria.

LV volumes and function

All MESA exam 5 CMR images were analyzed for LV volumes and function in a core laboratory and at a single image analysis center by readers blinded to clinical outcomes as previously described.[20,21] For quality control purposes, all readers independently analysed every tenth consecutive CMR exam. For exam 5, the overall interobserver intraclass correlation coefficients (ICC) for LV mass and LV end-diastolic volume were 0.95 and 0.96, respectively, and technical errors of measurement were 6.1% and 5.4%, respectively.

LA volume

CMR examinations were evaluated for biplanar or SAX LA volumes using the post-processing software tool cvi42 (Circle Cardiovascular Imaging Inc, Calgary, Canada). A single reader - a physician with over 3 years experience in CMR (FZ) - evaluated all images.

Horizontal and vertical long axis cine SSFP images were used for measuring the biplanar LA volume in LV end-systole, just before mitral valve opening (Figure 1). Participants with clear off-axis acquisition (n=416) of either plane were excluded from the analysis. Horizontal and vertical long axis cine sequences acquisition was planned to symmetrically assess the LV, therefore in 13.8% cases the LA was not fully visualised in these planes, making it impossible to accurately measure the LA volume.

Long-axis LV extent tool available on cvi42 was used to semi-automatically draw the initial LA contours by marking the mitral valve plane and the most distant point of the LA and then contours were adjusted manually. Pulmonary veins and LA appendage were excluded from the LA volume. LA area and LA height from both vertical and horizontal planes were used to calculate the biplanar LA volume using the formula:

LA Volume = 8 * Vertical Area * Horizontal Area / (3 * PI * ((Vertical Length + Horizontal Length)/2))[22]

LA contours on the SAX were drawn using a thresholding tool and then adjusted manually in 360 individuals from one of the MESA centres (Wake Forest University, Winston Salem), in whom both sequences were available (Figure 1E). LA volume was calculated using Simpson's rule (the summation of areas on each separate slice multiplied by the sum of slice thickness and image gap).

Indexed parameters (e.g., LA volume index) were calculated by dividing each parameter (e.g., LA volume) by body surface area (BSA). LA volume was indexed to other allometric measures

(weight, height, height$^{1.7}$, height$^{2.7}$ and fat-free mass) to assess differences between ethnicities and this data is presented in the supplement (Figure S1).

Biplanar volume was also measured on 198 randomly selected individuals who underwent both SSFP and fGRE cardiac pulse sequences (Figure 1C and 1D). Measurements of 100 randomly selected studies for biplanar LA volume, 40 randomly selected studies for SAX volume and 20 randomly selected studies for fGRE were repeated by the first reader and by a second reader to quantify intra- and inter-observer variability.

STATISTICAL ANALYSIS

Descriptive statistics for continuous variables are presented as mean and standard deviation (SD) if normally distributed. Categorical variables are presented as percentages. We used separate univariable linear regression models to calculate the association of LA volume index as the dependent variable with demographic and cardiovascular risk factors, LV parameters, diagnosis of coronary heart disease and antihypertensive therapy as independent variables. Multivariable regression models were then utilized to examine the association of LA volume index with independent variables. Model 1 assessed demographic and cardiovascular risk factors, model 2 used additional LV structural parameter (to avoid co-linearity we used end-diastolic volume, as it showed the strongest association with LA volume index; models with end-systolic volume index, ejection fraction and mass index are presented in the supplement), model 3 extended model 2 by antihypertensive pharmacotherapy and history of coronary heart disease. Model 4 extended model 3 by education and is presented in the supplement.

Univariable summary statistics were used to report normal reference values of LA volume

indexed to BSA by age, gender, and ethnicity. The upper limit of LA volume was defined as mean plus 2 SD.   Paired Student t-tests were performed to evaluate the difference between biplanar and short axis stack measurements of LA volume, and between fGRE and SSFP sequences. Linear regression models provided correlation estimates as well as slope and intercept estimates of the association between fGRE and SSFP measures. Separate two-way mixed models were used to estimate the ICC between techniques, sequences and two readers. The limits of agreement between measurements were compared using the Bland–Altman analysis.

Separate two-way ANOVA were used to compare gender differences in LAVi between ethnicities and age groups in participants free of cardiovascular diseases. Unpaired t-test was used to compare gender differences in LAVi between ethnicities while defining normal ranges in participants free of cardiovascular risk factors.

RESULTS

Subject demographics

Demographic and CMR data are presented in Table 1. The mean age of participants was 68.7 years (53.0% women). Ethnicity was self-reported as Caucasian/white in 42.3%, Chinese American in 12.0%, African-American/black in 24.5% and Hispanic in 21.2%. Hypertension was present in 56.7% of participants.

Four hundred and forty-six participants (17.3%) had treated diabetes and 1377 (53.7%) were current or former smokers.

Left atrial volume index and cardiovascular risk factors

The unadjusted mean LA volume index in the whole cohort was 36.5 ± 11.4 ml/m^2 and was slightly smaller in men (35.9 ± 11.1 vs. 37.0 ± 11.6 ml/m^2, p<0.05). LA volume index was positively associated with age, with a slope of 1.8 ml/m^2 (4.9% from the mean, p<0.0001) per decade in the unadjusted model (Table 2). Chinese Americans had smaller LA volume index compared to other ethnicities (Whites 36.8 ± 12.1 ml/m^2, Chinese Americans 33.3 ± 9.6 ml/m^2, African Americans 37.7 ± 10.5 ml/m^2, Hispanics 37.6 ± 11.5 ml/m^2, p<0.0001). These differences were seen also when other allometric measures were used to index LA volume (Supplement Figure S1).

Participants with hypertension had larger LA volume index (37.7 ± 12.2 vs. 35.0 ± 10.1 ml/m^2, p<0.0001). Presence of coronary artery disease (n=84) did not account for larger LA volume index (Table 3). Diabetes, smoking and obesity (defined as BMI≥30) were not associated with LA volume index, however, non-indexed LA volume was larger in smokers (β=3.1, p<0.0001) and in obese participants (β=8.4, p<0.0001) (Supplement Table S1). Total cholesterol, low-density lipoproteins (LDL), triglycerides and total cholesterol to high-density lipoprotein (HDL) ratio (TCh/HDL) were associated with smaller LA volume index, while higher HDL correlated with larger LA volume index. TCh/HDL had the strongest association with LA volume index and was used in the multivariable regression models.

In the fully adjusted model age, female gender, Hispanic ethnicity, obesity and left ventricular end-diastolic volume index were major determinants of larger LA volume index, while Chinese American ethnicity was associated with smaller LA volume index (Table 3). Interestingly, Hispanic ethnicity was not associated with non-indexed LA volume (Supplement Table S2) and

LA volume index after including socioeconomic factors (education) in the regression model (Supplement Table S3). Obesity was not associated with LA volume index in the models including LV end-systolic volume index and mass index (Supplement Table S4 and S5).

Left atrial volume index and left heart structure and function

The LA volume index was greater with larger LV volume in the fully adjusted model 3: by 0.4 ± 0.02 ml/m^2 for each ml/m^2 larger end-diastolic volume index (p<0.0001). There was no association of LA volume index with LV ejection fraction (p=0.39) in the unadjusted (Table 2) or fully adjusted models. LV hypertrophy, defined as LV mass index >78 g/m^2 in women (n=60) and >90 g/m^2 in men (n=121), was associated with significantly larger LA volume index (44.5 ± 15.7 vs. 35.9 ± 10.8 ml/m^2, p<0.0001).

Left atrial volume index and pharmacotherapy

In the fully adjusted model 4, the therapy with any antihypertensive agent was associated with greater LA volume index (β=1.2, p<0.05), but interestingly the presence of hypertension was not a determinant of LA volume index (β=0.6, p=0.36) in this model either. However, there was a strong association of hypertension with LA volume index in model 1 (β=1.8, p<0.0001) and model 2 (β=1.6, p<0.0001). These finding are explored in the discussion.

Left atrial volume and volume index in the reference cohort

The demographic data of this group are presented in Table 1.

The mean LA volume was 59.5 ± 17.8 ml and LA volume index was 35.5 ± 10.1 ml/m^2. Non-indexed LA volume was higher in men than women (62.7 ± 18.7 vs. 57.4 ± 16.9 ml, p<0.05,

respectively), but this difference disappeared when LA volume was adjusted to BSA: men 34.3±9.9 ml/m^2, women 36.2±10.2 ml/m^2 (p=0.13). LA volume in the reference cohort was not determined by height, weight, body surface area and BMI (Supplement Table S6). LA volume index was lower in Chinese Americans compared with Caucasians (p<0.05), but there were no differences between other ethnicities. Normal values for 4 ethnicities in MESA are presented in the table (Supplement Table S7). There were no significant differences in LA volume index between age categories (p=0.23). (Supplement Table S8)

Technical validation and reproducibility

Comparison of LA volume data derived from biplanar or short axis stack method

LA volume index from the biplanar measurement (37.3±10.3 ml/m^2) was only 0.8 % smaller than that analysed by short axis imaging and Simpson's rule (37.6±10.1 ml/m^2), p<0.05. LA volumes determined using these two methods were strongly correlated (ICC=0.97, 95%CI 0.96 to 0.97, p<0.0001). (Figure 2)

Comparison of LA volume data derived from fGRE and SSFP pulse sequences

The mean LA volume index measured by SSFP (36.0±11.0 ml/m^2) was 3% larger than by fGRE (34.9±11.3 ml/m^2), p < 0.001. There was an excellent agreement between SSFP and fGRE methods with ICC of 0.93 (95%CI 0.91 to 0.95), confirmed also on the Bland-Altman analysis (Figure 3). The linear regression model to estimate the SSFP values based on the fGRE measures yielded the following formula for conversion: SSFP LA volume = 0.91 x fGRE volume + 7.73.

Reproducibility and variability

There was excellent intraobserver reproducibility of biplanar method with ICC 0.96 (95%CI 0.94 to 0.97, p<0.0001). The mean difference between the measurements was 0.47±5.3 ml. Similarly, there was excellent intraobserver reproducibility of fGRE measurements with ICC 0.94 (95%CI 0.83 to 0.98, p<0.0001) and of the short axis stack measurements with ICC 0.98 (95%CI 0.96 to 0.99, p<0.0001).

The interobserver variability was excellent for all three used methods used for LA volume measurement: biplanar ICC 0.96 (95%CI 0.89 to 0.98, p<0.0001 – Figure 4), fGRE ICC 0.97 (95%CI 0.88 to 0.99, p<0.0001) and short axis stack ICC 0.96 (95%CI 0.92 to 0.98, p<0.0001)

DISCUSSION

To our knowledge, this is the first study describing LA volume in a large multi-ethnic population-based study. Age, female gender, Hispanic ethnicity and LV end-diastolic volume index were major determinants of larger LA volume index, while Chinese American ethnicity was associated with smaller LA volume index. Greater LA volume index was seen in participants with LV hypertrophy. After indexing to body size, LA volumes were similar in men and women. LA volumes were 3% larger when measured by SSFP versus FGRE cine CMR. Diabetes, smoking and obesity were not associated with LA volume index. We have defined the upper limit of normal (mean+2SD) for LA volume index values in individuals free of known cardiovascular disease as 56.4 ml/m^2 in females and 54.3 ml/m^2 in males, with specific values for four ethnicities (Supplement S5).

Comparison with previous studies

The mean LA volume index that we derived (35.5 ml/m^2) was about 11% smaller than previously reported by Maceira et al. (40 ml/m^2).[14] Habibi et al. used CMR tissue tracking in MESA to measure LA volume index in 224 healthy individuals on an older CMR fGRE sequences, deriving an average volume of 33 ml/m^2.[23] This study found SSFP volumes were about 3% larger than fGRE, resulting in mean fGRE volume of 34 ml/m^2, similar to volumetric LA analysis from Habibi et al.[23] Results from Hudsmith et al. are discrepant, with reported to be 97 ± 27 ml, vs. 59.5 ± 17.8 ml in our cohort.[15] We excluded CMR examinations with clear off-axis acquisitions, made possible through the availability of a cross-reference tool. The "gold-standard" volumetric measurement of LA volume was possible in the subgroup of 362 participants with SAX cine stack covering LA, while long-axis cine images allowing the biplanar measurement were available in all MESA participants. The mean difference between two techniques in our study was minimal (0.6%), which proved to be better compared to a previous report by Hudsmith et al., however the latter was performed on a smaller number of participants.[24] In contrast to Hudsmith at al. we have chosen to describe LA volume indexed to BSA, as this parameter has been historically used to account for body size and is the most sensitive in predicting cardiovascular outcomes.[25]

Gender

Gender did not influence LA volume index in the reference cohort free of cardiovascular disease, which is consistent with previous CMR and echocardiographic studies in adults[14,26-27] but also in children and adolescents.[28]

In the entire studied cohort, males tended to have smaller LA volume index – by 9% from a mean after adjusting for demographic data, risk factors, LV structural parameters and antihypertensive therapy (Table 3). This highlights the advantage of large cohort studies, which are sufficiently powered to detect subtle changes, which may not be seen in smaller studies.

Age

LA volume index was greater by 0.2 ml/m^2 per year, corresponding to about 5.5% LA volume increase per decade. The variation of LA volume with age was small and therefore very likely missed by studies with smaller number of participants.[14,29] Age related changes were seen in larger study by Boyd et al., who showed that LA volume index was greater by 0.05 ml/m^2 per year, but only became significant in the eighth decade.[27] Similarly, in the large echocardiographic study of 1480 healthy participants, D'Andrea et al. showed that LA size varies with age being significantly greater only in participants over 50 years of age.[26]

Ethnicity

In MESA, LA volume was smaller in Chinese American population and this was also observed after indexing to various allometric measures: BSA, height, height[1.7] (Supplement Figure S1). This appears to be largely a consequence of their overall smaller heart size, which has been previously shown in MESA by Natori et al., who reported lower LV mass and volumes in Chinese Americans compared with other ethnic groups.[21] Similarly, lower LA volume index have been seen in Indian Asian participants in a relatively large echocardiographic study by Chahal et al.[30]

Other factors affecting LA volume

The non-indexed LA volume was not associated with BMI, and in fact with any other allometric measures in the reference cohort free from cardiovascular disease, but was higher by 14% in obese participants with BMI≥30. The LA volume index was associated with obesity only in the adjusted model using LV end-diastolic volume index, but not other LV parameters. This is consistent with previous reports.[31]

Participants with dyslipidemia had minimally smaller LA volume index in the fully adjusted models including LV end-systolic volume index and LV end-diastolic mass index as independent variables (Supplement Tables S1 and S2). Although statistically significant, variation in LA size with dyslipidemia was small and unlikely to be of clinical significance. Hypertension was strongly associated with LA volume index in the unadjusted model, but also in models including demographic and LV structural parameters. In the fully adjusted model with antihypertensive therapy, only antihypertensive therapy, but not hypertension was associated with larger LA volume. This may suggest that severity of hypertension affects the LA volume.

Limitations

The study needs to be interpreted within its cross-sectional study context. The studied population age was between 54 and 94 years at the time of exam therefore we cannot determine the associations of LA volume in a younger population. Mitral regurgitation on CMR was not assessed in this study. Echocardiographic assessment was not available in MESA.

CONCLUSIONS

Age, gender, ethnicity and LV structural parameters were major determinants of LA volume index. Greater LA volume index was also seen in participants with LV hypertrophy and obesity. We have provided reference values of normal LA volume index in MESA population.

be found at http://www.mesa-nhlbi.org.

Disclosures:

None

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Figure 1: Measurement of left atrial volume in left ventricular systolic phase. A and B – SSFP horizontal and vertical long axis cine images, C and D – fGRE horizontal and vertical long axis cine, E – SSFP short axis cine sequence.
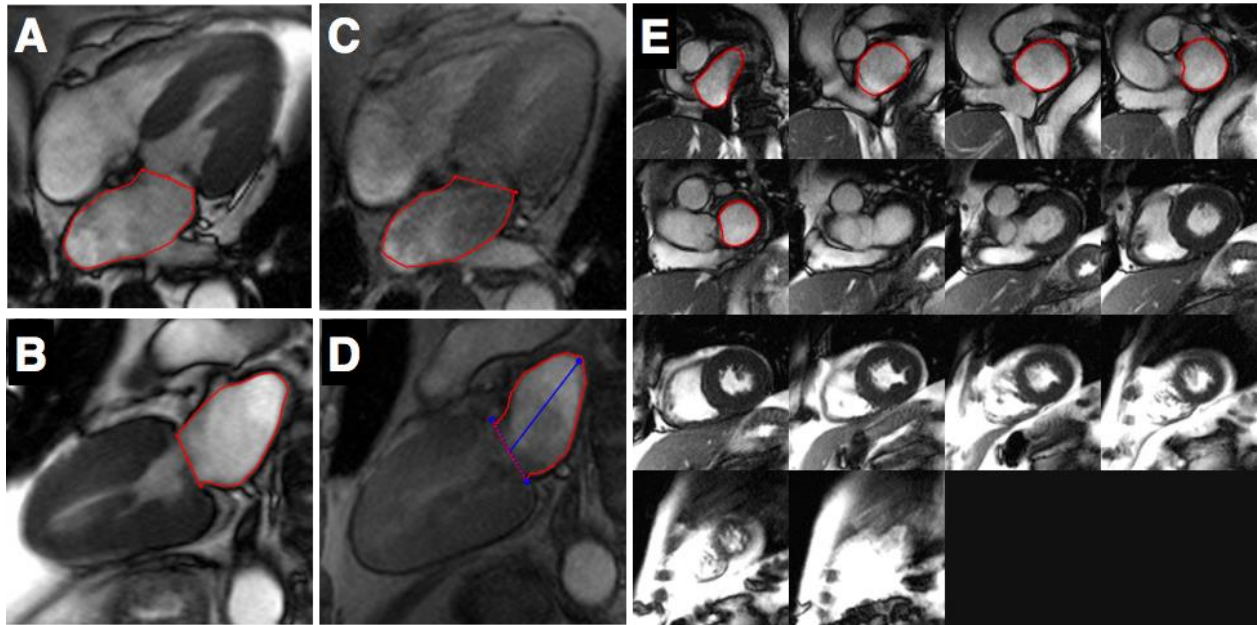
Figure 2: Comparison of LA volume index derived from the short axis stack (SAX) and biplanar methods using Bland-Altman plot. SD – standard deviation.
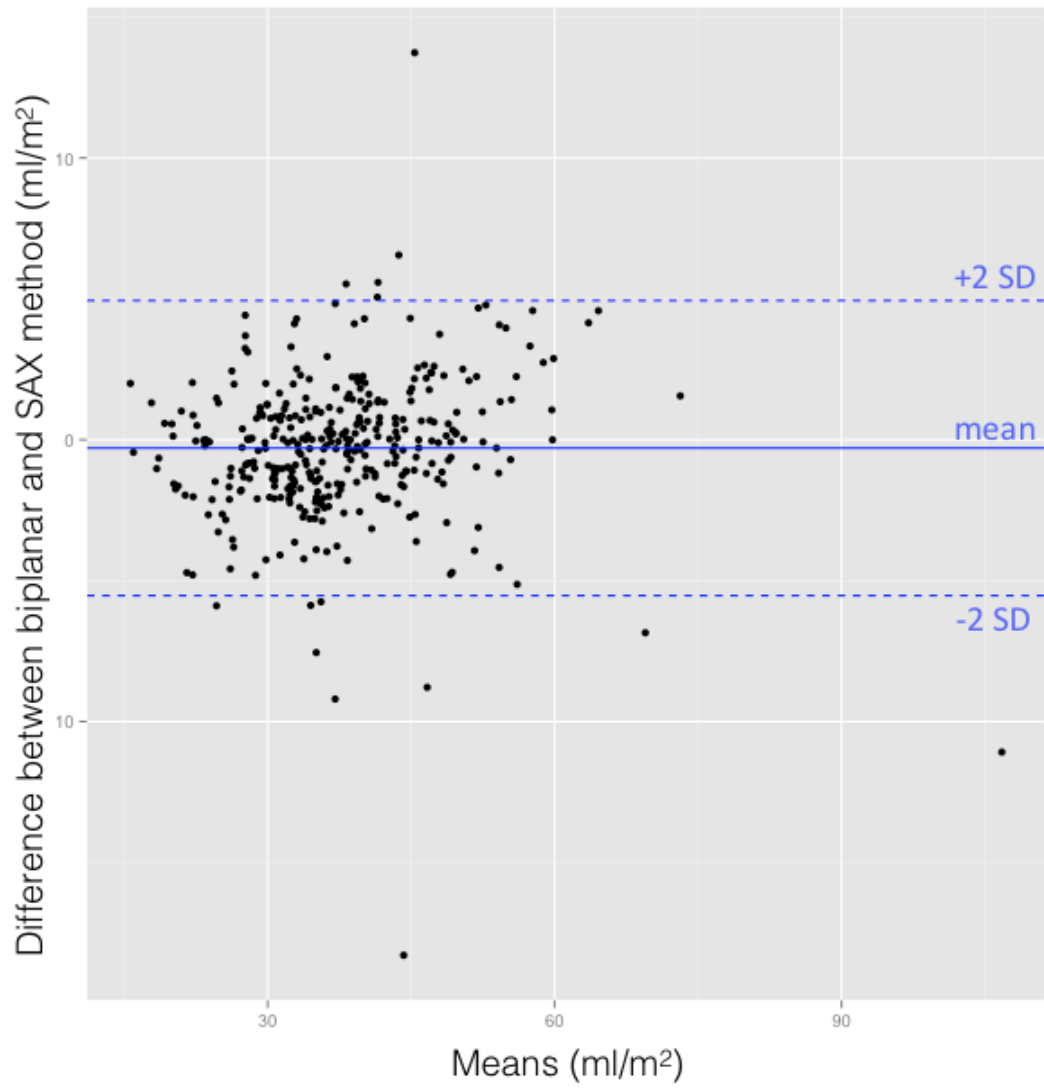
Figure 3: Comparison of LA volume index derived from biplanar measurements on SSFP and fGRE using Bland-Altman plot. SD – standard deviation
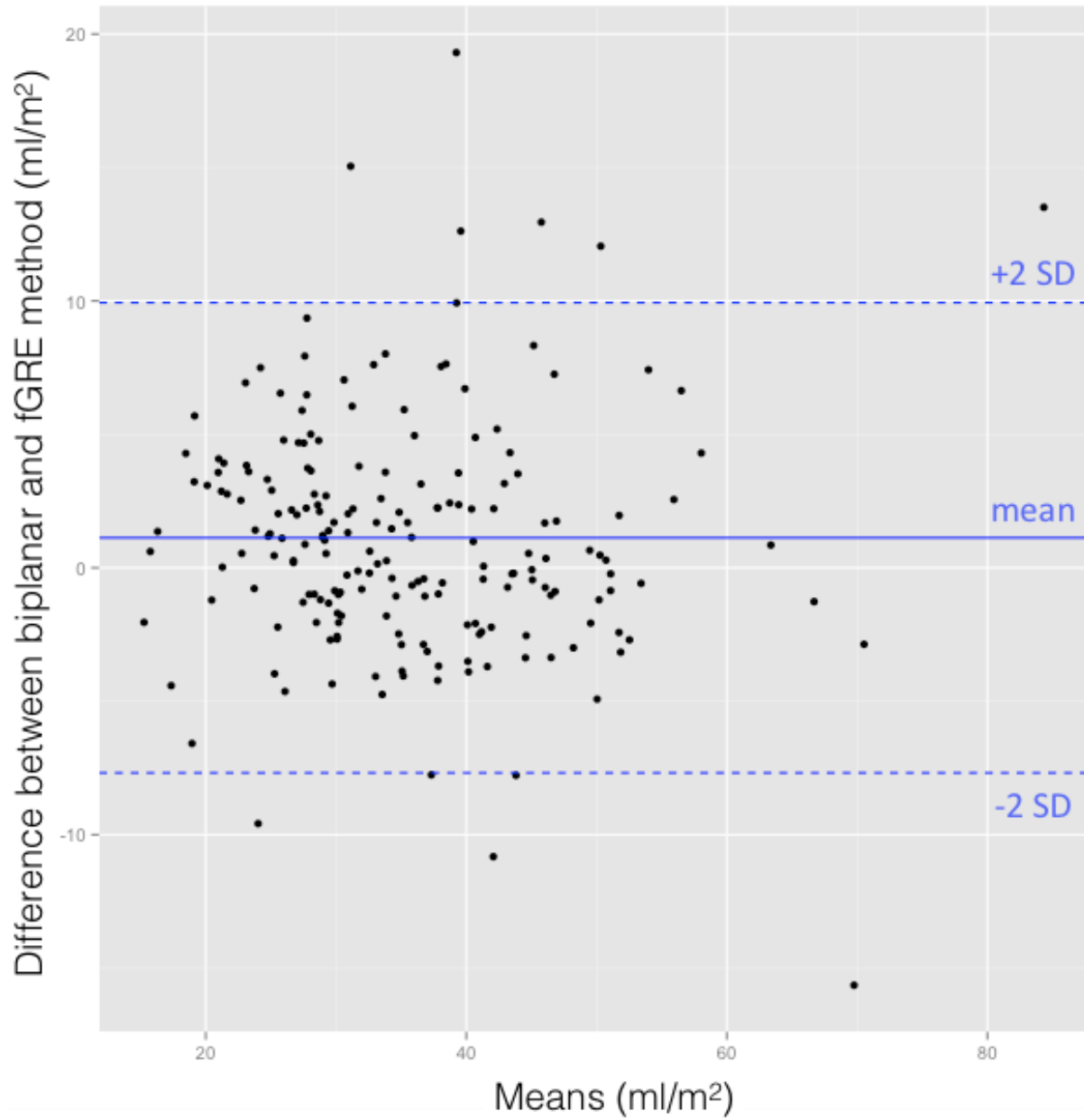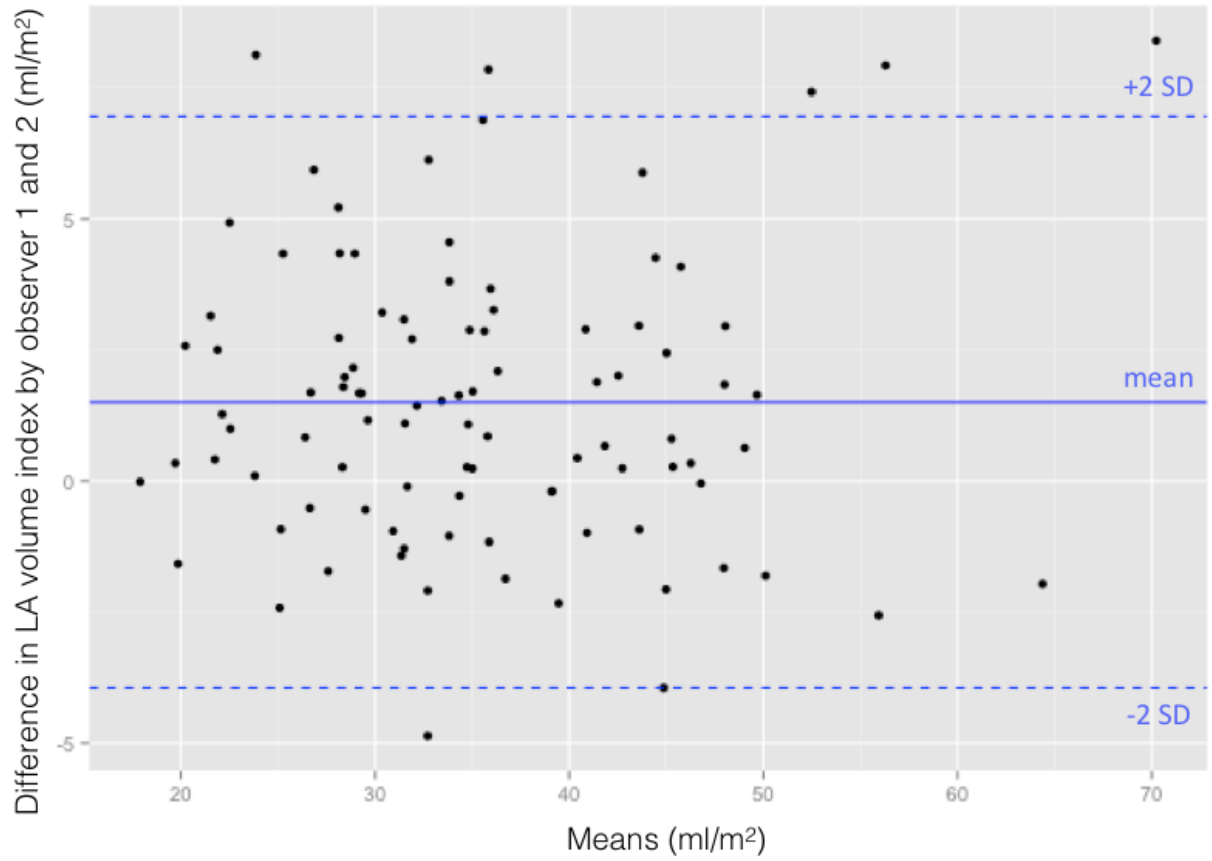
Figure 4: Bland-Altman analysis demonstrating an excellent inter-observer variability in biplanar measurement of the LA volume index. SD – standard deviation.

Table 1: Demographic characteristics.

	All participants	"Normal" participants*	Remaining "not normal" cohort
n	2576	283	2293
Age	68.7±9.1	65.4±8.5	69.1±9.1
Females (%)	1364 (53)	174 (61.5)	1190 (51.9%)
Race			
Caucasian (%)	1089 (42.3)	164 (57.9)	925 (40.3)
Chinese American (%)	310 (12.0)	62 (21.9)	248 (10.8)
Black, African-American (%)	631 (24.5)	26 (9.2)	605 (26.4)
Hispanic (%)	546 (21.2)	31 (11.0)	515 (22.5)
Height (cm)	165.5±9.9	165.2±9.6	165.6±9.9
Weight (kg)	77.3±16.6	61.6±9.2	79.3±16.3
Body mass index (kg/m^2)	28.1±5.1	22.5±1.7	28.8±5.0
Education (n=2571)			
No school	10 (0.4)	1 (0.4)	9 (0.4)
Grades 1-8	199 (7.7)	16 (5.7)	183 (8.0)
Grades 9-11	118 (4.6)	6 (2.1)	112 (4.9)
Completed High School	428 (16.6)	28 (9.9)	400 (17.4)
Some College but no degree	423 (16.5)	42 (14.8)	381 (16.6)
Technical School Certificate	185 (7.2)	19 (6.7)	166 (7.2)
Associate Degree	127 (4.9)	16 (5.7)	111 (4.8)
Bachelor's Degree	513 (20.0)	72 (25.4)	441 (19.2)
Graduate or Professional School	568 (22.1)	83 (29.3)	485 (21.2)
Hypertension	1460 (56.7)	-	1460 (100%)
Systolic blood pressure (mmHg)	122.8±20.0	108.9±14.0	124±20.0
Diastolic blood pressure (mmHg)	68.3±9.8	64.7±8.8	68.7±9.8
Diabetes by 2003 ADA**			
Normal (%)	1599 (62.1)	283 (100)	1316 (57.4)
Impaired Fasting Glucose (%)	531 (20.6)	-	531 (23.2)
Untreated Diabetes (%)	33 (1.3)	-	33 (1.4)
Treated Diabetes (%)	413 (16.0)	-	413 (18.0)
Atrial fibrillation (%)	31 (1.2)	-	31 (1.4)
Family history of a heart attack (%)	1049 (43.1)	87 (30.7)	962 (42.0)
Coronary disease (%)	84 (3.3)	-	84 (3.7)
Smoking			
Never (%)	1187 (46.3)	182 (100)	1035 (45.4)
Former (%)	1184 (46.2)		1078 (47.3)
Current (%)	193 (7.5)		168 (7.4)
LV end-diastolic volume index (ml/m^2)	64.9±13.6	66.7±11.0	64.7±13.9
LV end-systolic volume index (ml/m^2)	24.9±8.5	25.1±6.1	24.8±8.7
LV stroke volume index (ml/m^2)	40.0±8.3	41.5±7.1	39.9±8.4
LV ejection fraction (%)	62.1±7.2	62.5±5.6	62.1±7.4
LV mass index (g/m^2)	66.3±13.6	60.1±10.6	67.0±13.8

*Normal participants: with normal BMI (≥18.5 and < 25 kg/m^2), without hypertension, diabetes, coronary heart disease, heart failure, LV systolic dysfunction (defined as ejection fraction <50%), left ventricular hypertrophy or atrial fibrillation. **ADA: American Diabetes Association

Table 2: Unadjusted linear regression models showing associations of LA volume index with cardiovascular disease risk factors in 2576 MESA participants

	β ml/m²	95%CI	p
Age (per 10 years)	1.8	1.3 to 2.3	<0.0001
Male gender	-1.1	-2.0 to -0.2	<0.05
Ethnicity (vs. white)			
Chinese American	-3.5	-4.9 to -2.1	<0.0001
African American	-0.1	-1.2 to 1.0	0.88
Hispanic	0.8	-0.3 to 2.0	0.16
Obesity (BMI >30)	0.1	-0.8 to 1.0	0.82
Systolic blood pressure (per mmHg)	0.06	0.04 to 0.08	<0.0001
Diastolic blood pressure (per mmHg)	-0.1	-0.15 to -0.06	<0.0001
Hypertension	2.7	1.9 to 3.6	<0.0001
Cigarette smoking (current and former)	-0.04	-0.93 to 0.84	0.92
Diabetes	-0.6	-1.7 to 0.6	0.35
Total cholesterol (mg/dl)	-0.03	-0.04 to -0.01	<0.0001
HDL (mg/dl)	0.06	0.04 to 0.09	<0.0001
LDL (mg/dl)	-0.03	-0.04 to -0.02	<0.0001
Triglycerides (mg/dl)	-0.03	-0.03 to -0.02	<0.0001
Total cholesterol/HDL ratio	-1.52	-1.93 to -1.11	<0.0001
Coronary heart disease	3.5	1.1 to 6.0	<0.01
Previous myocardial infarction	0.9	-2.7 to 4.5	0.63
Antihypertensive therapy	2.4	1.6 to 3.3	<0.0001
End-diastolic volume index (per ml/m²)	0.36	0.33 to 0.39	<0.0001
End-systolic volume index (per ml/m²)	0.38	0.33 to 0.43	<0.0001
Ejection fraction (per %)	-0.03	-0.09 to 0.03	0.372
LV mass index (per g/m²)	0.2	0.17 to 0.23	<0.0001
LV hypertrophy*	8.6	6.9 to 10.3	<0.0001

*LV mass index >78 g/m² in women and >90 g/m² in men

Table 3: Adjusted linear regression models showing associations (β) of LA volume index with exposure

variables.

	Model 1 ml/m²	Model 2 ml/m²	Model 3 ml/m²
Age (per year)	**0.1*****	**0.3*****	**0.2*****
Male gender	-0.4	**-4.1*****	**-4.2*****
Ethnicity (vs. white)			
Chinese American	**-3.1*****	**-2.6*****	**-2.6*****
Black, African-American	-0.4	-0.9	-0.8
Hispanic	1.1	**1.1#**	**1.1#**
Obesity (BMI ≥ 30)	0.3	**1.4***	**1.3***
Smoking (log-transformed pack years)	**-0.4#**	-0.2	-0.2
Hypertension	**1.8*****	**1.6*****	0.7
Diabetes	**-1.3#**	-0.3	-0.5
Total cholesterol to HDL ratio (per 1 unit increase)	**-1.2*****	**-0.4#**	**-0.4**
End-diastolic volume index (per ml/m²)		**0.4*****	**0.4*****
Coronary heart disease			1.7
Antihypertensive therapy			1.2
R-square	0.055	0.28	0.29

\# - p<0.05, * - p<0.01, ** - p<0.001, *** - p<0.0001

Model 1: age, gender, ethnicity, obesity, smoking, hypertension, diabetes, total cholesterol to HDL ratio

Model 2: model 1 + end-diastolic volume index

Model 3: model 2 + history of coronary heart disease and antihypertensive therapy