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ORIGINAL RESEARCH

Population-Based Reference Values for 3D Echocardiographic LV Volumes and Ejection Fraction

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OBJECTIVES The purpose of this study was to define age-, sex-, and ethnicity-specific reference values for 3-dimensional echocardiographic (3DE) left ventricular (LV) volumes and LV ejection fraction (LVEF) in a large cohort of European white and Indian Asian subjects.

BACKGROUND Transthoracic 3DE imaging is recommended for the routine evaluation of LV volumes and function. However, there remains a lack of population-based reference values for 3DE LV volumes and LVEF, hindering adoption of this technique into routine clinical practice.

METHODS We identified subjects from the LOLIPOP (London Life Sciences Prospective Population) study who were free of clinical cardiovascular disease, hypertension, and type 2 diabetes. All subjects underwent transthoracic 2-dimensional and 3D echocardiography for quantification of LV end-systolic volume index, LV end-diastolic volume index, and LVEF.

RESULTS 3DE image quality was satisfactory in 978 subjects (89%) for the purposes of LV volumetric analysis. Indexed 3DE LV volumes were significantly smaller in female compared with male subjects and in Indian Asians compared with European whites. Upper limit of normal (mean ± 2 SD) reference values for the LV end-systolic volume index and LV end-diastolic volume index for the 4 ethnicity-sex subgroups were, respectively, as follows: European white men, 29 ml/m^2 and 67 ml/m^2; Indian Asian men, 26 ml/m^2 and 59 ml/m^2; European white women, 24 ml/m^2 and 58 ml/m^2; Indian Asian women, 23 ml/m^2 and 55 ml/m^2, respectively. Compared with 3DE studies, 2-dimensional echocardiography underestimated the LV end-systolic volume index and LV end-diastolic volume index by an average of 2.0 ml/m^2 and 4.7 ml/m^2, respectively. LVEF was similar between in all 4 groups and between 2- and 3-dimensional techniques, with a lower cutoff of 52% for the whole cohort.

CONCLUSIONS These reference values are based on the largest 3DE study performed to date that should facilitate the standardization of the technique and encourage its adoption for the routine assessment of LV volumes and LVEF in the clinical echocardiography laboratory. This study supports the application of ethnicity-specific reference values for indexed LV volumes. (J Am Coll Cardiol Img 2012; 5:1191–7) © 2012 by the American College of Cardiology Foundation

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ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

3D = 3-dimensional

3DE = 3-dimensional echocardiographic

BP = blood pressure

BSA = body surface area

CMR = cardiac magnetic resonance

CVD = cardiovascular disease

EF = ejection fraction

LV = left ventricular

LVEDVI = left ventricular end-diastolic volume index

LVEF = left ventricular ejection fraction

LVESVI = left ventricular end-systolic volume index

Transthoracic 3-dimensional (3D) echocardiography provides a rapid and accurate method for quantifying left ventricular (LV) volumes and left ventricular ejection fraction (LVEF) (1,2). It has a superior reproducibility to 2-dimensional (2D) echocardiography, with a closer correlation with cardiac magnetic resonance (CMR)–derived volumes (3,4). For these reasons, the European and American Echocardiography Associations recently recommended 3D, rather than 2D, echocardiography for the routine assessment of LV volumes and LVEF. However, the writing committee also acknowledged the need to establish 3D echocardiographic (3DE) reference values according to age, sex, and body size (5). The lack of reference values at present, together with a need to develop faster automation of LV contouring, has limited the adoption of 3DE assessment of LV function into routine clinical practice.

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We defined the reference values for 3DE volumes and LVEF in a large community-based, biethnic cohort, free of clinical cardiovascular disease (CVD), type 2 diabetes, and hypertension.

METHODS

We recruited Indian Asian and European white subjects between August 2004 and November 2007 from the LOLIPOP (London Life Sciences Prospective Population) study. LOLIPOP is a population study of ~30,000 Indian Asian and European white men and women 35 to 75 years of age recruited from the lists of 58 general practitioners in West London. The study design was previously described (6). Briefly, subjects successfully enrolled in the main LOLIPOP cohort were then invited at random to participate in the imaging substudy. The principal inclusion criteria were that subjects should be: 1) of Indian Asian or European white ethnicity; 2) 35 to 75 years of age; and 3) free of clinical CVD. Subjects with CVD were defined as individuals with either coronary artery disease (self-reported myocardial infarction or silent myocardial infarction [Minnesota criteria for Q waves], surgical/percutaneous coronary revascularization, or self-reported/physician-confirmed CVD) and/or any life-limiting illness. Subjects were defined as Indian Asian if all 4 grandparents were born in the Indian subcontinent and European white if all 4 grandparents were born in Northern Europe.

Approximately 2,300 subjects were then recruited to undergo 2D and 3D echocardiography as part of the imaging substudy. Consenting individuals provided a full medical history, underwent physical assessment, and blood pressure (BP) and anthropometric measurements. Office BP was measured using an automated device with the subject in a seated position, with the average of 3 separate measurements at 1-min intervals recorded as the resting BP. For the purposes of this study, individuals with a history of hypertension (office BP >140/90 mm Hg, treatment for hypertension) and

Table 1. Clinical and Echocardiographic Variables of the Cohort

	All (N = 978)	European White Men (n = 338)	Indian Asian Men (n = 290)	European White Women (n = 161)	Indian Asian Women (n = 189)
Age, yrs	54 ± 10	54 ± 9	52 ± 10*	55 ± 10	53 ± 10
sBP, mm Hg	120 ± 11	124 ± 10	121 ± 10†	116 ± 12	115 ± 11
dBP, mm Hg	76 ± 7	77 ± 7	77 ± 7	73 ± 8	73 ± 6
BMI, kg/m^2	26 ± 4	27 ± 4	26 ± 3†	26 ± 5	27 ± 5*
BSA, m^2	1.9 ± 0.2	2.0 ± 0.2	1.9 ± 0.2‡	1.8 ± 0.2	1.7 ± 0.2‡
3DE LVESVI, ml/m^2	17 ± 5	19 ± 5	16 ± 5‡	16 ± 4	15 ± 4*
3DE LVEDVI, ml/m^2	44 ± 10	49 ± 9	41 ± 9‡	42 ± 8	39 ± 8†
3DE LVEF	62 ± 5	61 ± 6	62 ± 5	62 ± 5	62 ± 5
2DE LVESVI, ml/m^2	15 ± 5	17 ± 5	14 ± 4	14 ± 4	13 ± 4
2DE LVEDVI, ml/m^2	39 ± 10	44 ± 9	36 ± 8	38 ± 9	33 ± 8
2DE LVEF	62 ± 6	61 ± 5	62 ± 6	63 ± 5	63 ± 5

Values are mean ± SD. *$p < 0.05$ when comparisons made between European white men with Indian Asian men, and between European white women with Indian Asian women. †$p < 0.01$ when comparisons made between European white men with Indian Asian men, and between European white women with Indian Asian women. ‡$p < 0.001$ when comparisons made between European white men with Indian Asian men, and between European white women with Indian Asian women.
2DE = 2-dimensional echocardiographic; 3DE = 3-dimensional echocardiographic; BMI = body mass index; BSA = body surface area; dBP = diastolic blood pressure; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; sBP = systolic blood pressure.

type 2 diabetes were excluded from further analysis. The study was approved by the Northwick Park and Ealing Hospitals Research Ethics Committees.

3D echocardiography. All subjects underwent transthoracic 2D echocardiography, as previously described (7), which included online measurement of left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), and LVEF, using the biplane method of disks. Indexing of LV volumes was performed to body surface area (BSA). Real-time 3D echocardiography was performed immediately afterward using a matrix array ultrasonic transducer (X3-1 transducer, Philips IE33, Philips Medical Systems, Holland, the Netherlands). 3DE images were obtained with the subject in the left lateral position over 4 cardiac cycles during a breath-hold. Echocardiographic studies were performed at a single center by 3 cardiology fellows (N.S.C., T.K.L., P.J.) who were all experienced 2D echocardiographers and who all underwent a 4-wk period of training in 3DE volume acquisition and off-analysis by the vendor representative at the beginning of the study.

Measurement of 3DE LV volumes was performed offline (Q-Lab 5, Philips Medical Systems) by 2 fellows (N.C., T.K.L.), blinded to the 2D volume and LVEF measurements. End-diastolic and end-systolic frames were identified using the electrocardiogram. Contour tracing was performed with semiautomatic border detection after first identifying the apex and 4 mitral annular points (septal, lateral, anterior, and inferior). A 3D endocardial shell of the entire left ventricle was then produced from which LV volumes were calculated and BSA indexed measurements derived for 3DE LVEDVI and LVESVI.

Both 2D and 3D studies were repeated separately, and offline analysis was performed independently by 2 sonographers (N.C., P.J.) in 15 subjects to assess reproducibility. The coefficients of variation for LVESVI, LVEDVI, and LVEF using both techniques were calculated.

Statistical analysis. Clinical and echocardiographic data were stratified according to ethnicity and sex, with European white men and women serving as reference groups for comparison with Indian Asian men and women respectively. Analysis of variance was used to test differences of continuous variables with Bonferroni's correction for multiple comparisons.

Partition values for increased LVESVI and LVEDVI, stratified according to ethnicity-sex sub-

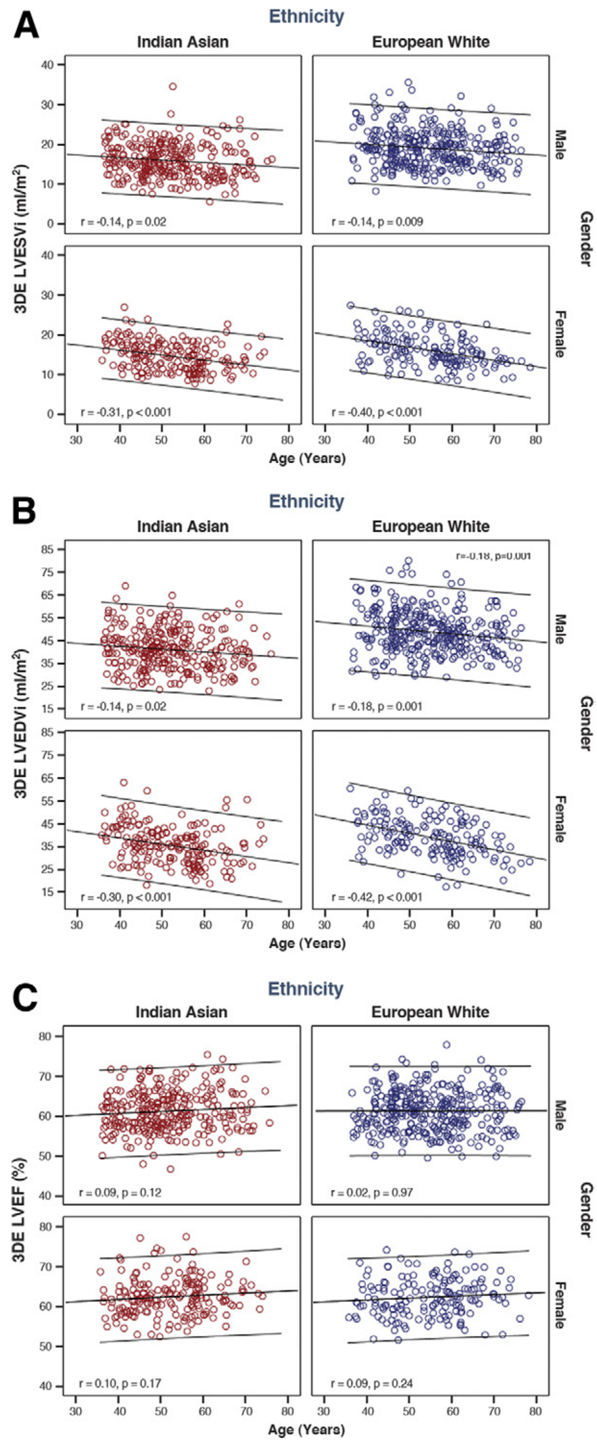

Figure 1. Distribution of Values for 3DE LVESVI, 3DE LVEDVI, and 3DE LVEF According to Ethnicity, Gender, and Age

(A) 3DE LVESVI; **(B)** 3DE LVEDVI; and **(C)** 3DE LVEF. Fitted regression lines with 95% confidence intervals are presented stratified according to ethnicity-sex subgroups, with Pearson's correlation coefficient (r) and p values. 3DE = 3-dimensional echocardiographic; LV = left ventricular; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index.

Table 2. Reference Values for 3-Dimensional Echocardiographic LV Volumes and Ejection Fraction, Stratified by Age, Ethnicity, and Sex

Age, yrs	European White Men				Indian Asian Men				European White Women				Indian Asian Women			
	n	LVESVI	LVEDVI	LVEF	n	LVESVI	LVEDVI	LVEF	n	LVESVI	LVEDVI	LVEF	n	LVESVI	LVEDVI	LVEF
35–44	56	30	72	50	68	28	63	50	33	26	64	52	50	23	59	53
45–54	128	32	71	52	128	24	57	51	40	26	59	51	59	21*	53	52
55–64	99	29	64	48	63	23*	55*	51	62	21*†	56*†	53	61	19*	49*†	53
65–75	55	26	62†	47	31	24	56	53	26	20*†	52*†	55	19	22*	60	55

Reference values defined as mean ± 2 SD for LV volumes and mean −2 SD for LVEF. *$p < 0.05$ versus 35 to 44 years of age. †$p < 0.05$ versus 45 to 54 years of age within an ethnicity-sex subgroup.
Abbreviations as in Table 1.

groups, are presented as the mean + 2 SD. Stepwise linear regression analysis was performed to assess the independent associations of clinical and demographic variables with 3DE volumes and LVEF. Agreement between 2D echocardiographic and 3DE measurements of LV volumes and LVEF was assessed by performing Bland-Altman analyses. Spearman's correlation coefficients (r) were also calculated for these variables with age.

RESULTS

Of the 2,293 subjects recruited for the imaging substudy, 1,106 individuals fulfilled the criteria for the purposes of this investigation, being free of hypertension, type 2 diabetes, and manifest CVD. Of these individuals, satisfactory 3DE images for the purposes of LV volume quantification were feasible in 978 subjects (89%).

The mean age was 54 years, with 50% being of European white ethnicity and 63% being male. Table 1 displays clinical and echocardiographic variables for the cohort, stratified according to ethnicity and sex. Indian Asian men were significantly younger and had lower systolic BP than European white men. Indian Asians had significantly lower body mass index and BSA compared with European whites.

Measured 3DE LVEF was similar between ethnicity-sex subgroups (Table 1) and showed only a weak positive correlation with increasing age (Fig. 1A). Both mean 3DE LVESVI and LVEDVI indexed to BSA were smaller among Indian Asian men and women compared with their European white counterparts. Mean ± 2SD reference values for 3DE LVESVI, LVEDVI, and LVEF stratified by ethnicity-sex subgroups are presented in Table 2. Modest negative correlations were observed for both systolic and diastolic volumes with increasing age, which was more pronounced among women than men (Figs. 1A and 1B). There was a weak positive correlation between increasing age and LVEF that was further attenuated in European white men (Fig. 1C).

The strength of the relationships between demographic and clinical covariates with 3DE LV volumes and LVEF were assessed (Tables 3 and 4). Ethnicity was most closely associated with LV volumes, which were significantly smaller among Indian Asians. Increasing age, female sex, and increasing diastolic BP were also associated with significantly smaller volumes, whereas increasing systolic BP was associated with higher volumes. Only sex was significantly associated with 3DE LVEF, being higher among women than men (Table 4).

Compared with 3D echocardiography, Bland-Altman analyses revealed 2D echocardiography to consistently underestimate both LVEDVI and LVESVI by an average of 2 ml/m^2 and 4.7 ml/m^2, respectively (Figs. 2A and 2B). Two-SD limits of

Table 3. Independent Correlates of 3DE Volumes Using Stepwise Linear Regression

Covariate	3DE LVESVI		3DE LVEDVI	
	β Coefficient	p Value	β Coefficient	p Value
Indian Asian ethnicity	−0.29	<0.001	−0.36	<0.001
Age	−0.22	<0.001	−0.23	<0.001
Female	−0.22	<0.001	−0.21	<0.001
dBP	−0.13	0.008	−0.14	0.001
sBP	0.11	0.02	0.12	0.007

Abbreviations as in Table 1.

Table 4. Independent Correlates of 3DE LVEF Using Stepwise Linear Regression

Covariate	β Coefficient	p Value
Female	0.11	<0.001
Age	0.06	0.11
Indian Asian ethnicity	0.03	0.45
dBP	0.01	0.83
sBP	−0.01	0.77

Abbreviations as in Table 1.

agreement values were ±13.4 ml/m^2 for EDVI and ±7.6 ml/m^2 for ESVI, resulting in potential underestimation of 3D volumes by 2D echocardiography of as much as 18.1 ml/m^2 and ±9.6 ml/m^2 for EDVI and ESVI, respectively.

The mean difference between 3DE LVEF and 2D echocardiographic LVEF was very small, with narrower limits of agreement compared with volumes (−0.43 ± 5.9%), as also illustrated in Figure 2C.

Interobserver variability between the 2 techniques was similar; the coefficients of variation for the LVESVI, LVEDVI, and LVEF for 2D echocardiography were 9.9%, 5.8%, and 3.6%, respectively, and for 3D echocardiography, they were 5.8%, 8%, and 3.7%, respectively.

DISCUSSION

We present reference values for 3DE LV volumes and LVEF derived from the largest 3D echocardiography cohort study to have been conducted, with subjects being free of clinical CVD, hypertension, and diabetes. The proposed cutoff values are presented as the mean ± 2 SD, stratified according to ethnicity, sex, and age, conforming to the agreed-on convention regarding the standardization and generation of reference values for cardiac structures (8).

The mean 3D indexed volumes reported in this study are smaller than previously published values from validation studies. However, the majority of patients enrolled in these studies warranted CMR imaging to further investigate manifest LV remodeling due to coronary artery disease or cardiomyopathy. A recent meta-analysis of these studies demonstrated that considerable variability still exists between 3DE and CMR measurements of LV volumes (±34 ml for end-diastolic volume, ±30 ml for end-systolic volume, and ±12% for ejection fraction [EF]), although it is less than that observed between 2D echocardiography and CMR (9). Moreover, both 2D and 3D echocardiography–

Figure 2. Bland-Altman Analyses of the Agreement Between 3DE Versus 2D Echocardiographic Measurements of LVESVI, LVEDVI, and LV EF

(A) LVESVI; **(B)** LVEDVI; and **(C)** LV EF. Differences are plotted against mean values **(solid line)** with their limits of agreement (±2 SD, **dashed lines**). EDVI = end-diastolic volume index; ESVI = end-systolic volume index; other abbreviations as in Figure 1.

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derived volumes are less accurate in dilated left ventricles compared with CMR (10).

Assessment of LV volumes by 2D echocardiography is limited by foreshortening, malrotation, angulation, and a reliance on geometric assumptions for volumetric calculation, resulting in an underestimation of the true volumes, particularly in remodeled ventricles (4). In this study of healthy subjects without a history of myocardial infarction or evident LV dysfunction, Bland-Altman analyses revealed 2D echocardiography to systematically underestimate the end-systolic volume index by as much as 9.6 ml/m^2 and end-diastolic volume index by as much as 18.1 ml/m^2 compared with 3DE measurements and falls within the range of variability observed in the meta-analysis published by Dorosz et al. (9).

We have confirmed findings of previous studies, namely, the strong association of LV volumes with age and sex. Indexed LV volumes are known to be inversely associated with advancing age and to be lower among women, even after indexing for body size (11). We previously reported data from this cohort, highlighting the importance of ethnicity-specific reference values for LV volumes (7). We again observed indexed 3DE volumes to be significantly smaller among Indian Asians compared with European whites, even after adjustment for age and sex.

Despite the significant associations of demographic variables with LV volumes, their associations with LVEF were weaker, highlighting the relative insensitivity of the EF as a tool to detect alterations in LV remodeling processes (12).

We found the measurement of LV volumes and LVEF using 3D echocardiography to be a reproducible technique, with a coefficient of variation between operators of <8% for volumetric assessment and <4% for EF, similar to the error observed in comparative measurements using 2D echocardiography.

Study limitations. We demonstrated a significant relationship between 3DE LV volumes and age in this study, but because the LOLIPOP study design precluded enrollment of subjects 18 to 35 years of age, we were unable to provide reference values for this age group.

We obtained all 3D studies using a single vendor platform and its proprietary analysis algorithm, which has implications for the applicability of these reference values to volumetric datasets that are acquired or analyzed with other vendor platforms.

Although the 3DE images are rapidly acquired, volumetric analysis is performed offline and can be time-consuming and prone to stitching artifact and require expertise. Recently, a fully automated endocardial contouring system combined with real-time full-volume 3D echocardiography has been described as providing accurate and reproducible volumes (13), although the software is not yet commercially available.

CONCLUSIONS

We present reference values for 3DE LV volumes and LVEF, which should facilitate 3D echocardiography to become part of the routine assessment of LV function in the clinical laboratory. This study supports the application of ethnicity-specific reference values for indexed LV volumes.

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Key Words: 3-dimensional echocardiography ■ ejection fraction ■ left ventricular volumes ■ reference values.