Original Article

Global longitudinal strain, ejection fraction, effort tolerance and normal echocardiography measurements in healthy Indians

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**ABSTRACT**

Introduction: Normative comprehensive echocardiographic measurements data for healthy Indians are not available while data for American and European population is available from American Society of echocardiography and European Society of Cardiology/European Association of Cardio-Vascular Imaging and their publications. Available studies of Indian subjects are small and report only limited measurements with focus on left ventricular (LV) volumes.

Objective: We aim to provide comprehensive normative echocardiographic data for healthy Indians from a large sample size.

Methods: A retrospective cross-sectional single-center study of 707 healthy Indian adults age and sex segregated which presented detailed and comprehensive echocardiographic measurements including two-dimensional, M-mode, tissue Doppler imaging, speckle tracking echocardiography, chamber volumes, LV ejection fraction (LVEF), global longitudinal strain (GLS), segmental longitudinal strain and effort tolerance.

Results: Our findings show healthy Indians, as compared to US and European population, to have higher relative wall thickness. LV volumes, LV mass, LVEF and effort tolerance that were within American Society of Echocardiography described ranges for chamber quantification. Higher GLS values were observed in Indian population compared to European and American population. Women had higher LVEF and GLS values as compared to men and both showed a gradual decline with aging.

Conclusion: We present normal reference values for echocardiographic measurements in healthy Indian population, which could be used for future reference and comparison work.

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1. Introduction

Echocardiography is the most widely used non-invasive real time cardiac imaging modality. Quantitative measurements data derived from echocardiography requires normal reference values for interpretation and application in clinical practice. Normative reference values of echocardiographic measurements for American and European populations are available from American Society of Echocardiography (ASE) and European Society of Cardiology (ESC)/ European Association of Cardio-Vascular Imaging (EACVI) and their publications.\textsuperscript{1,2,5,8} Chahal et al\textsuperscript{2} compared two-dimensional (2D) and three-dimensional (3D) echocardiography derived values of left ventricular (LV) volumes and LV ejection fraction (LVEF). They showed healthy Indian Asians to have smaller LV volumes but similar LVEF as compared to European whites. Recognizing the ethnic/racial differences of echocardiographic measurements, Bansal et al\textsuperscript{3} recently reported in an Indian pilot study similar differences with western data while providing LV volumes and diastolic parameters.

Emergence of speckle-tracking echocardiography (STE) has provided a simple means to measure global longitudinal strain (GLS), which is an objective and reproducible measure of LV systolic function and has been shown to have incremental value over LVEF. Normal values for GLS and LVEF have been reported earlier in various studies, with a large population-based HUNT study in Norway\textsuperscript{1} serving as a large reference-base. Unfortunately, such comprehensive normative echocardiographic data is not available for Indians. We, hereby aim to fill this gap by describing GLS, LVEF, effort tolerance and normative echocardiography data in

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a population of 707 healthy Indians, having no known cardiovascular disease and no basic echocardiographic abnormality, which could be compared to international standards and used as reference values.

2. Methods

2.1. Study design and population

This was a retrospective cross-sectional single-center study of 707 healthy Indian adults who underwent comprehensive echocardiography, including measurement of global and segmental longitudinal strain, and assessment of effort tolerance. Age- and sex-specific normative values of various measurements were calculated. The values were also compared with those reported for the western populations. Study subjects were people who randomly came for a cardiac medical check-up, had no cardiovascular disease history and consented. About 4903 echocardiography studies were done from May 2015 to July 2016 at our hospital. Subjects who had any cardiovascular disease and their basic echocardiography study was having any congenital, valvular (except trivial regurgitation), cardiomyopathy (dilated, ischaemic, hypertrophic, infiltrative or restrictive), ischemic wall motion abnormalities, arrhythmias, diastolic abnormalities and abnormal systolic LV function were excluded as these could have influenced their echocardiography derived data. Only subjects having normal systolic and diastolic ventricular functions and who underwent a Stress test were included for analysis. 908 normal studies were found. Only studies with optimal imaging and speckle tracking (>15/17 LV segments clearly definable and trackable) were included as our aim was to obtain normative reference values in healthy Indian subjects. 201 studies (22.1%) with suboptimal imaging were rejected. 707 echocardiography studies of healthy Indians were retrospectively selected from our database. Systolic blood pressure of all subjects was <140 mmHg. Diastolic blood pressure of all subjects was <90 mmHg.

The study was approved by our institution’s Ethical committee and conducted according to the Helsinki declaration. Written informed consent for anonymous use of data for scientific academic purposes was taken from all subjects.

2.2. Examination

Echocardiography studies were performed by an experienced physician echocardiologist on a Philips Epiq 7C echocardiography system, Koninklijke Philips, Andover, MA, USA, using an X5-1 transducer. The studies were performed, and measurements taken as per ASE guidelines and Comprehensive Trans-Thoracic Echocardiography examination guidelines by Indian Academy of Echocardiography. The echocardiography/Doppler examination was performed in parasternal long and short axis views and the three standard apical views. Three consecutive cardiac cycles were recorded during quiet respiration in Each view in left lateral decubitus at A frame rate of 50–70 fps. Separate grey-scale second harmonic mode (at mean frame rate 44 fps) and color tissue Doppler mode (at mean frame rate 100 fps) were recorded at the three apical planes. Doppler pulse repetition frequency was 1 kHz. 2D parasternal long axis End systolic left atrial (LA) diameter and End diastolic mid right ventricular (RV) diameter were measured as linear measurements. M-mode Echocardiography in left parasternal long axis view was used to measure LV End-diastolic diameter (LVEDD), LV End-systolic diameter (LVEDS), Interventricular septal thickness (IVS) in diastole and LV posterior wall thickness (PW) in diastole. Apical 4-chamber M-mode Echocardiography at lateral tricuspid annulus was used to measure tricuspid annular plane systolic Excursion (TAPSE). Mitral E velocity, deceleration time (Dtc) and E/A ratio were obtained using pulsed Doppler spectral recording at tips of mitral valve in apical four chamber view. S’, S’ and A’ velocities were measured at medial mitral annulus and S’ at lateral tricuspid annulus, using tissue Doppler imaging (TDI). LA end systolic Volume (LVEDV), LV end diastolic Volume (LVEDV), LV end systolic Volume (LVESV) and LVEF were measured using Simpson’s biplane (two and four chamber views) method of discs in end-diastolic and end-systolic frames. On-line 2D speckle tracking echocardiography (STE) was performed using ECG gating on the three standard apical views (four chamber, two chamber and three chamber views) using automated cardiac motion quantification (ACMQ) on Q-Lab software installed on the Epiq 7C system. The software automatically tracked the myocardial motion and operator manually adjusted the myocardial limits if automated tracking was incorrect. STE generated Regional LS in ASE defined 17 standard LV myocardial segments were recorded and averaged to generate GLS. Echocardiography studies’ data were stored digitally in aDicom server. Data generated from these studies was used for our analysis. Indexing to body surface area (BSA by Mosteller formula) was done offline for LA vol (LAVI), LV Mass, LVEDV (LVEDVI) and LVESV (LVESVI).

Effort Tolerance was measured in metabolic equivalents (METS), which was obtained when subjects underwent an exercise Tolerance test on Bruce Protocol on a Tread Mill system – GE Case premium T2100 V6.72, GE Medical Systems, 8200 West Tower Avenue, Milwaukee, WI, USA, by an experienced technician under direct supervision of physician. The predetermined end points of exercise testing were a positive test or maximal exercise capacity. Heart rate was recorded from a continuous 12-lead ECG monitoring. The age-predicted maximal heart rate was calculated as 220-age. Target heart rate was defined as 85% of the age-predicted maximal heart rate. The exercise time was recorded. Maximal exercise capacity was defined by the achieved metabolic equivalents (METs). Mets equal 3.5 mL of oxygen uptake per kilogram of body weight per minute and are estimated from exercise time as METs = 1.1 + (0.016 × exercise time in seconds). Patients with good exercise capacity were defined as those who achieved ≥7 METs.

2.3. Statistics

Statistical analysis was done using Statistical Package for the Social Sciences (IBM SPSS Statistics 20.0 Chicago, IL, USA). The level of significance for all tests was set at p < 0.05. The Shapiro-Wilk test was used to assess the distribution of data. Tests results showed normal distribution of data and thus further assessment of correlation was done using Pearson’s correlation coefficient. Independent t-test was used to compare male and female population variables.

2.4. Data reproducibility

Sixty echocardiography studies, 10 each from the age and sex segregated groups, (from the 707 studies) stored in our dicom digital server were retrieved. These were analyzed by a separate physician echocardiologist for inter-analyzer reproducibility and were re-analyzed by the primary physician echocardiologist for intra-analyzer reproducibility. Intra-class correlation coefficient (ICC) was assessed on IBM SPSS Statistics 20.0 Chicago, IL, USA.

3. Results

3.1. Study population

Seven hundred and seven subjects’ data was analyzed for the study. There were 444 males and 263 females. Age ranged from 18 years to 70 years. For the purpose of age related variation, they
LA: LA Volume, un-indexed and indexed to BSA, was within ASE described guidelines applicable for both males and females. LV volumes: In our total sample population, LV volumes both un-indexed and indexed to BSA were smaller in Indian adults compared to US adults but were within normal range as described by ASE. Indian females had slightly larger LV volumes compared to US adults but were within normal range as described by ASE guideline. LV mass, un-indexed and indexed to BSA, was mildly higher in Indian adults compared to older (>30 year age) Indian males. LV volumes of total Indian males however were smaller than US males but within ASE range. Similar age related variations are reported in ASE's data with younger adults having higher LV volumes compared to older population. LV wall thickness: LV wall thickness in Indian adults was found to be higher than US adults but they were within threshold of 1.2 cm to be classified as hypertrophy. Higher wall thickness and smaller LV volumes resulted in a higher relative wall thickness (RWT) compared to ASE guideline. LV mass: LV mass both un-indexed and indexed to BSA was within ASE guideline range in our total sample population. LV mass, un-indexed and indexed to BSA, was mildly higher in Indian females compared to US females but within normal range as described by ASE. LVEF: LVEF was comparable to ASE guidelines. (For normative echocardiography measurements comparisons, see Supplementary Table A).

GLS: GLS - Strain, a measure of deformation per length, is already normalized for LV size and further normalizing for body size is inappropriate.1 MESA study did not show any racial differences in Strain measurements, but it did not show any differences related to age or sex either.1 Our findings show higher values for Segmental and GLS in Indian population as compared to those reported in Hunt study and as reported by Marwick et al (For Global & Segmental longitudinal strain comparisons, see Supplementary Table B).

TDI: Mitral annular systolic tissue Doppler velocity, MV s' is another measurement of LV longitudinal myocardial shortening, which reflects LV function and a value of >7.5 cm/s predicting normal global LV systolic function. Normal range for septal MV s' is 8.1 ± 1.5 cm/s which correlates well with EF and GLS.1,9 Our values for MV s' were higher than earlier reported. TDI reference values for septal E/e', MV E/A and MV Dt are presented for reference of LV diastolic function.

RV: RV systolic function can be indirectly assessed with echocardiography by measuring the motion of lateral tricuspid annulus using M-mode echocardiography in tricuspid annular plane systolic excursion (TAPSE) and by TDI echocardiography in TV s' velocity. Our values for TAPSE and TV s' are presented for reference of RV function.

**Table 1**

| Echocardiography measurements data | Males and Females |
|-----------------------------------|-------------------|
| Total Sample Number 707           |                   |
| Males Number 444                  |                   |
| Females Number 263                |                   |
| Age Yr                            | Minimum | Maximum | Mean | Std Dev | Minimum | Maximum | Mean | Std Dev | Minimum | Maximum | Mean | Std Dev |
| Ht cm                             | 139.6    | 194.8   | 165.45| 10.05   | 171.16  | 18.94   | 1.72  | 18.36   | 21.5    | 16.18   | 19.05| 2.05   |
| Wt kg                             | 135.8    | 194.8   | 165.45| 10.05   | 171.16  | 18.94   | 1.72  | 18.36   | 21.5    | 16.18   | 19.05| 2.05   |
| BMI - kg/m²                       | 47.1     | 131.7   | 27.07 | 4.87    | 43.3    | 11.7   | 2.43  | 11.32   | 2.7     | 11.23   | 2.6  | 1.02  |
| BSA - m²                          | 258.8    | 131.7   | 184.01| 0.21    | 258.8   | 184.01 | 0.21  | 184.01  | 0.21    | 184.01  | 0.21 | 1.02  |
| E/e                              | 30.6     | 30.6    | 30.6  | 0.05    | 30.6    | 30.6   | 0.05  | 30.6    | 0.05    | 30.6    | 0.05 | 1.02  |
| LV Mass gm/mt²                   | 262.8    | 262.8   | 262.8 | 0.05    | 262.8   | 262.8  | 0.05  | 262.8   | 0.05    | 262.8   | 0.05 | 1.02  |
| TAPSE - cm/s                     | 23.2     | 23.2    | 23.2  | 0.05    | 23.2    | 23.2   | 0.05  | 23.2    | 0.05    | 23.2    | 0.05 | 1.02  |
| LV s' - cm/s                     | 5.65     | 5.65    | 5.65  | 0.05    | 5.65    | 5.65   | 0.05  | 5.65    | 0.05    | 5.65    | 0.05 | 1.02  |
| RV s' - cm/s                     | 1.7      | 1.7     | 1.7   | 0.05    | 1.7     | 1.7    | 0.05  | 1.7     | 0.05    | 1.7     | 0.05 | 1.02  |
| LA Diamt - cm                    | 4        | 4       | 4     | 0.05    | 4       | 4      | 0.05  | 4       | 0.05    | 4       | 0.05 | 1.02  |
| LA Vel - ml                      | 60.3     | 60.3    | 60.3  | 0.05    | 60.3    | 60.3   | 0.05  | 60.3    | 0.05    | 60.3    | 0.05 | 1.02  |
| LA Vel Indx ml/mt²               | 41.7     | 41.7    | 41.7  | 0.05    | 41.7    | 41.7   | 0.05  | 41.7    | 0.05    | 41.7    | 0.05 | 1.02  |
| LVESV ml                         | 42.02    | 42.02   | 42.02 | 0.05    | 42.02   | 42.02  | 0.05  | 42.02   | 0.05    | 42.02   | 0.05 | 1.02  |
| MITR s'                           | 1.7      | 1.7     | 1.7   | 0.05    | 1.7     | 1.7    | 0.05  | 1.7     | 0.05    | 1.7     | 0.05 | 1.02  |
| TV s' - cm/s                     | 23.2     | 23.2    | 23.2  | 0.05    | 23.2    | 23.2   | 0.05  | 23.2    | 0.05    | 23.2    | 0.05 | 1.02  |
| MV s'                            | 1.7      | 1.7     | 1.7   | 0.05    | 1.7     | 1.7    | 0.05  | 1.7     | 0.05    | 1.7     | 0.05 | 1.02  |
| MV Dt                            | 0.001*   | 0.001*  | 0.001 | 0.001*  | 0.001*  | 0.001* | 0.001*| 0.001*  | 0.001*  | 0.001*  | 0.001*| 0.001* |
| MITR s'                           | 1.7      | 1.7     | 1.7   | 0.05    | 1.7     | 1.7    | 0.05  | 1.7     | 0.05    | 1.7     | 0.05 | 1.02  |
| TV s' - cm/s                     | 23.2     | 23.2    | 23.2  | 0.05    | 23.2    | 23.2   | 0.05  | 23.2    | 0.05    | 23.2    | 0.05 | 1.02  |
| MV s'                            | 1.7      | 1.7     | 1.7   | 0.05    | 1.7     | 1.7    | 0.05  | 1.7     | 0.05    | 1.7     | 0.05 | 1.02  |
| MV Dt                            | 0.001*   | 0.001*  | 0.001 | 0.001*  | 0.001*  | 0.001* | 0.001*| 0.001*  | 0.001*  | 0.001*  | 0.001*| 0.001* |

**p < 0.05.**
Age and gender wise GLS Comparison

| Age Wise | Male | Female |
|----------|------|--------|
| <30 Yr   | 19.74 (±1.76) | 21.10 (±2.49) |
|          | (±2.0)        | (±2.1)       |
|          | <40 Yr        | <40 Yr       |
| 30-50 Yr | 19.62 (±2.07) | 20.74 (±2.2) |
|          | (±2.2)        | (±2.2)       |
|          | 40-60 Yr      | >60 Yr       |
| >50 Yr   | 19.46 (±2.07) | 20.21 (±2.63) |
|          | (±2.4)        | (±2.4)       |

Effort tolerance observed in METS while walking on a treadmill on Bruce protocol were within average Mets range reported by Jette et al in 1990. This did not show any significant correlation with EF or GLS in present study. There was a gradual age related decline in METS achieved. All subjects had normal echocardiography studies with normal cardiac functions and normal effort tolerance.

Intra-class correlation coefficient (ICC) values for intra-analyzer assessment ranged from 0.814 to 0.998 showing good to excellent reliability. For inter-analyzer assessment ICC values were 0.696 to 0.989 showing moderate to excellent reliability. For ICC values, see Supplementary Table C.

(Not: For Abbreviations used in Tables, see Supplementary Table D).

4. Discussion

Earlier studies have shown that ethnicity is an important determinant of cardiac chamber sizes. Indians have been shown to have smaller chamber sizes than Europeans but equivalent LVEF.\(^2\) It was observed earlier that LVESVI and LVEDVI indexed to BSA were smaller in Indian Asian men and women compared with their European white counterparts while LVEF was similar between ethnicity-sex subgroups.\(^2\) It was also observed previously that indexing to BSA reduced the LVEDV and LVEFS differences between Indian measurements and ASE defined normal considerably.\(^3\) These references make a strong point for collection of different population based normative data useful for comparison and reference by medical community.

Normative measurements have been established by ASE and EACVI and we have tried to compare our results with them (Supplementary Table A and B). It is interesting to observe that LV volume measurements reported in decreasing order of volumes are highest in Hunt\(^1\) European data, followed by ASE\(^5\) American data, our Indian data, Bansal et al\(^3\) Indian data, Chahal et al\(^2\) European data, and Chahal et al\(^3\) Indian data. All quoted studies have used biplane method of discs except Hunt study where Teicholz method was used for LV volume. Despite using the same method, differences are there even in Indian subject studies, which may be explored in future. If we look at ASE\(^5\) data, similar differences have been reported in various studies included in their guidelines for chamber quantification. LV volumes un-indexed and indexed to BSA in our data were within ASE\(^5\) specified range.

We have observed mildly thicker LV walls which however are not classifiable in hypertrophy category based on thickness. LV
Both men and women showed a decline in these metrics with increasing age. Women showed smaller LVESV, LVEDV, and LV mass while higher LVEF and GLS as compared to men. Both men and women showed a decline in these metrics with aging. These findings are similar to those reported in Hunt study.¹

5. Limitations

This is a study done in central India representing a small fraction of our population. Sub-ethnic data segregation was not attempted as that would better be addressed in a larger multicenter study. Study subjects were people who randomly came for a medical check-up and gave consent. It is a single center retrospective data study where all echocardiography examinations were performed by a single physician. Detailed cardiovascular risk factor analysis was not possible due to retrospective nature of the study and we cannot ensure all subjects to be free of risk factors or free of subclinical cardiovascular disease. The study was done on single vendor equipment and findings have been compared to studies done with equipment by a different vendor as reported in other studies. GLS software technology is hidden from the user and not yet standardised between commercially available machines of different vendors. Recently 3D echocardiography is shown superior to 2D echocardiography for determining LV volumes and LVEF but these echocardiography systems are not yet widely available in India and comprehensive normative 2D data was yet not available. 2D echocardiography underestimates LVEDVI by 2 ml/m² and LVESVI by 4.7 ml/m² compared to 3D echocardiography.² Also, the difference between 3D echocardiography and 2D echocardiography derived LVEF was very small – 0.43%.²

6. Conclusion

We present normal reference values for echocardiography measurements in healthy Indian population which could be used for future reference and comparison work. We found in our study that healthy Indians as compared to US and European population have thicker LV walls (though not classifiable as hypertrophy), higher RWT (which probably needs an upper cut-off revision to 0.47 instead of 0.42 recommended by ASE). LV volumes, LV Mass, LVEF and effort tolerance were within ASE described ranges for chamber quantification. Higher GLS values were observed in Indian population compared to European and American population.

Women had higher EF and GLS values as compared to men and both showed a gradual decline with aging. These findings need to be supplemented by random sampled population based multicentered Indian data.

Disclosure

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What is Already Known?

Indians have smaller LV volumes but equivalent LVEF as compared to Europeans and Americans.

What this Study Adds?

Comprehensive normative echocardiography data for comparison and reference is presented for Indian adults, which as of yet were not available.?