Reference Ranges for Left Ventricular Curvedness and Curvedness-Based Functional Indices Using Cardiovascular Magnetic Resonance in Healthy Asian Subjects

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Curvature-based three-dimensional cardiovascular magnetic resonance (CMR) allows regional function characterization without an external spatial frame of reference. However, introduction of this modality into clinical practice is hampered by lack of reference values. We aim to establish normal ranges for 3D left ventricular (LV) regional parameters in relation to age and gender for 171 healthy subjects. LV geometrical reconstruction and automatic calculation of regional parameters were implemented by in-house software (CardioWerkz) using stacks of short-axis cine slices. Parameter normal ranges were stratified by gender and age categories (≤ 44, 45–64, 65–74 and 75–84 years). Our software had excellent intra- and inter-observer agreement. Ageing was significantly associated with increases in end-systolic (ES) curvedness ($C_{ES}$) and area strain (AS) with higher rates of increase in males, end-diastolic (ED) and ES wall thickness ($WT_{ED}, WT_{ES}$) with higher rates of increase in females, and reductions in ED and ES wall stress indices ($\sigma_{i,ED}$) with higher rates of increase in females. Females exhibited greater ED curvedness, $C_{ES}$, $\sigma_{i,ED}$ and AS than males, but smaller $WT_{ED}$ and $WT_{ES}$. Age × gender interaction was not observed for any parameter. This study establishes age and gender specific reference values for 3D LV regional parameters using CMR without additional image acquisition.

Structural and functional changes occur in the left ventricle (LV) during disease processes and over the course of chronological ageing. Cardiac magnetic resonance (CMR), specifically Simpson’s method employing phasic endocardial border contouring of a stack of parallel LV short-axis two-dimensional (2D) cine CMR images, is long regarded as the gold standard for quantification and assessment of global LV function and volumes due to its superiority over other modalities like echocardiography in terms of imaging quality, accuracy and reproducibility. Current CMR feature tracking (FT) techniques allow characterization of LV regional — and when aggregated, global — function, but are ultimately still based on tracking of 2D cine CMR images, commonly the LV basal, mid-cavity and apical short-axis slices. The spatially spread-out 2D image slices constitute a sparse sampling of LV geometry and can neither capture changes in LV deformation in their entirety nor account for through-plane displacements. To comprehensively quantify LV geometry and longitudinal changes associated with remodeling in disease or with ageing, three-dimensional (3D) techniques potentially offer greater sensitivity and precision. This will be particularly helpful for the challenging task of quantitative characterization of LV geometry.

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alterations among non-diseased healthy male and female subjects of various age groups, who do not exhibit gross LV remodeling.

In our previous studies, regional ventricular curvedness, thickness, curvature-based wall stress index and area strain were automatically evaluated from 3D reconstructed LV geometry in diverse of LV pathologies such as ischemic dilated cardiomyopathy, heart failure (HF), myocardial infarction and hypertrophic cardiomyopathy, as well as predominant right ventricular pathophysiology such as repaired tetralogy of Fallot. In this study, we hypothesize that our 3D technique can be applied in healthy cohorts to characterize gender- and age-related differences in LV geometry. Our results will provide reference values for the 3D characterization technique which will facilitate future clinical applications in healthy cohorts for both genders across various age groups.

Results

Baseline demographics of study population. The analysis cohort comprised 171 subjects without prior history of cardiovascular disease, hypertension, dyslipidemia or diabetes, and with LV ejection fraction (EF) ≥ 50% on CMR. Demographic data were collected at the time of imaging. In the evaluation of age-related characteristics, subjects were stratified into the four age (M/F) groups based on definitions of young, mid-age, young-old and middle-old by the Department of Statistics Singapore: <44 years (30/36), 45–64 years (16/22), 65–74 years (30/23) and 75–84 years (7/7).

Table 1 summarizes the baseline demographics, clinical and CMR-derived LV parameters of study subjects (Appendix Table 1 tabulates the comparison of same parameters based on age groups of 10 years: 20–29 years; 30–39 years; 40–49 years; 50–59 years; 60–69 years; ≥ 70 years). The mean age was 52 ± 19 years; 83 (49%) were 45–64 years, 65–74 years (30/23) and 75–84 years (7/7).

Table 1 summarizes the baseline demographics, clinical and CMR-derived LV parameters of study subjects. ANOVA indicated statistically significant differences among four age groups for CES, σES, σED, i,ES and AS (all P < 0.05). There were significantly higher CES, i,ES and AS for those aged 75–84 years compared with the other three age groups (P < 0.05). The 45–64 years, 65–74 years and 75–84 years age groups showed significantly lower σES compared with the ≤44 years age group. Shaded error plots (mean ± SD) for CED, CES, WTED, WTES, σED, σES, and AS for individual LV wall segments among the age groups are given in Figure 2.

Comparisons of 3D regional parameters by age and gender. Regional parameters for CED, σED, σES, i,ED, i,ES and AS (all P < 0.05). There were significantly higher CED and AS for those aged 75–84 years compared with the other three age groups (P < 0.05). The 45–64 years, 65–74 years and 75–84 years age groups showed significantly lower σES compared with the ≤44 years age group. Shaded error plots (mean ± SD) for CED, CES, WTED, WTES, σED, σES, and AS for individual LV wall segments among the age groups are given in Figure 2.

Comparisons of 3D regional parameters between males and females are presented in Table 2. CED, CES, σED, σES and AS were significantly larger in females (CED, 0.042 ± 0.004 mm−1; CES, 0.071 ± 0.010 mm−1; σED, 2.89 ± 0.47; AS, 72 ± 11%) compared with males (CED, 0.039 ± 0.004 mm−1; CES, 0.066 ± 0.011 mm−1; σED, 2.55 ± 0.38; AS, 67 ± 11%) (all P < 0.003). No significant differences were seen for σLES and σES between genders (male vs female: σLES, 0.96 ± 0.23 vs 1.01 ± 0.24; σES, 15.8 ± 3.7 vs 15.6 ± 3.5 1000 N/m2). Gender comparisons of CED, CES, WTED, WTES, σED, σES, and AS in individual LV segments are presented in Figure 3. Per segment comparisons of CED and CES showed significant differences at the following segments: basal anterior (Segment 1); inferior, inferior lateral and anterior lateral (Segments 4–6); mid anterior septal (Segment 8); inferior lateral (Segment 11); and apical anterior (Segment 13) (all P < 0.05). For wall thickness, females exhibited significantly thinner myocardial walls than males at both ED and ES for all segments (all P < 0.05) except for apical inferior at ES phase. For σES with the exception of basal anterior septal (Segment 2) and mid inferior (Segment 10), no differences were found at other segments or aggregated values at basal, mid-cavity and apical levels. The basal and mid-cavity anterior lateral segments, and the apical lateral segment, had the largest σES. There were no differences between males and females in AS, with the exception of the apical septal segment (Segment 14).

Interaction of age × gender with 3D regional parameters. Table 3 summarizes the results of 3D regional parameters stratified by gender and age groups (<44, 45–64, 65–74 and 75–84 years). CED (P = 0.0067), CES (P = 0.0001) and AS (P < 0.0001) increased significantly with age, while σLES (P = 0.0160) and σES (P = 0.0011) decreased with age. Results of male vs female comparisons of ANOVA least squares means are as follows: CED (0.040 vs 0.042 mm−1, P = 0.0042), CES (0.068 vs 0.073 mm−1, P = 0.0077), σLES (2.52 vs 2.81, P = 0.0002) and AS (68 vs 74%, P = 0.0006) were significantly lower in males than females; conversely, WTES (5.29 vs 4.62 mm, P < 0.0001) and WTES (8.17 vs 7.53 mm, P = 0.0022) were significantly higher in males than females. No gender differences were found in least squares means (male vs female) for σLES (0.93 vs 0.97, P = 0.344) or σES (15.3 vs 15.2 1000 N/m2, P = 0.808). Figure 4 presents box plots of CED, CES, WTED, WTES, σED, σES, and AS vs
| Parameters                      | Total (n = 171) | ≤ 44 (Young) (n = 66) | 45–64 (Mid-age) (n = 38) | 65–74 (Young-Old) (n = 53) | 75–84 (Medium-Old) (n = 14) | P Value |
|--------------------------------|-----------------|------------------------|--------------------------|-----------------------------|----------------------------|---------|
| Male, n (%)                    | 83 (48.5%)      | 30 (45.5%)             | 16 (42.1%)               | 30 (56.6%)                  | 7 (50.0%)                  | NS      |
| Age, years (range)             | 52 ± 19         | 31 ± 7 (20–44)         | 55 ± 6* (45–64)          | 70 ± 3* (65–74)             | 76 ± 1** (75–84)           | <0.001  |
| Ethnicity, n (%)               | 154 (90.1%)     | 53 (80.3%)             | 34 (89.5%)               | 53 (100%)                   | 14 (100%)                  | 0.001   |
| Smoking, n (%)                 | 0.001           | 0.001                  | 0.001                    | 0.001                       | 0.001                      |         |
| Chinese                        | 154 (90.1%)     | 53 (80.3%)             | 34 (89.5%)               | 53 (100%)                   | 14 (100%)                  |         |
| Malay                          | 7 (4.1%)        | 5 (7.6%)               | 2 (5.3%)                 | 0 (0%)                      | 0 (0%)                     |         |
| Indian                         | 2 (1.2%)        | 1 (1.5%)               | 1 (2.6%)                 | 0 (0%)                      | 0 (0%)                     |         |
| Others                         | 8 (4.7%)        | 6 (9.1%)               | 1 (2.6%)                 | 0 (0%)                      | 0 (0%)                     |         |
| Height, cm                     | 163 ± 9         | 165 ± 10               | 162 ± 7                  | 162 ± 8                     | 158 ± 7*                   | 0.008   |
| Weight, kg                     | 61 ± 12         | 63 ± 15                | 64 ± 12                  | 59 ± 9                      | 55 ± 7                     | 0.042   |
| Body surface area, m²          | 1.66 ± 0.20     | 1.70 ± 0.25            | 1.69 ± 0.19              | 1.63 ± 0.15                 | 1.54 ± 0.11*               | 0.022   |
| Body mass index, kg/m²         | 23.0 ± 3.3      | 22.9 ± 3.5             | 24.0 ± 3.3               | 22.6 ± 2.9                  | 22.2 ± 3.4                 | 0.205   |
| SBP, mmHg                      | 135 ± 20        | 126 ± 15               | 130 ± 18                 | 146 ± 20**                  | 146 ± 22**                 | <0.001  |
| DBP, mmHg                      | 77 ± 10         | 75 ± 11                | 79 ± 9                   | 79 ± 10                     | 74 ± 8                     | 0.056   |
| Heart rate, bpm                | 76 ± 12         | 77 ± 12                | 74 ± 12                  | 76 ± 13                     | 79 ± 11                    | 0.526   |
| LV EDV index, ml/m²            | 69 ± 11         | 74 ± 10                | 70 ± 10                  | 66 ± 10*                    | 55 ± 8**                   | <0.001  |
| LV ESV index, ml/m²            | 25 ± 7          | 28 ± 7                 | 24 ± 5*                  | 24 ± 7                      | 18 ± 4**                   | <0.001  |
| LV stroke volume index, ml/m³   | 44 ± 7          | 45 ± 6                 | 46 ± 8                   | 42 ± 6                      | 37 ± 7**                   | <0.001  |
| LV ejection fraction, %        | 64 ± 6          | 62 ± 6                 | 64 ± 6                   | 64 ± 7                      | 67 ± 6*                    | 0.011   |
| LV mass index, g/m²            | 45 ± 11         | 45 ± 11                | 47 ± 10                  | 45 ± 11                     | 39 ± 7                     | 0.151   |
| LV mass-to-volume ratio, g/ml   | 0.65 ± 0.16     | 0.61 ± 0.15            | 0.66 ± 0.15              | 0.69 ± 0.16*                | 0.72 ± 0.11                | 0.017   |
| ED curvedness, mm⁻¹            | 0.041 ± 0.004   | 0.040 ± 0.004          | 0.041 ± 0.004            | 0.040 ± 0.004               | 0.043 ± 0.003              | 0.072   |
| ES curvedness, mm⁻¹            | 0.068 ± 0.011   | 0.066 ± 0.011          | 0.069 ± 0.009            | 0.068 ± 0.011               | 0.078 ± 0.012*             | 0.002   |
| ED wall thickness, mm          | 4.92 ± 0.77     | 4.80 ± 0.72            | 4.92 ± 0.67              | 5.03 ± 0.80                 | 5.01 ± 0.80                | 0.425   |
| ES wall thickness, mm          | 7.75 ± 1.22     | 7.46 ± 1.20            | 7.88 ± 0.92              | 7.95 ± 1.34                 | 8.08 ± 1.42                | 0.089   |
| ED wall stress index           | 2.72 ± 0.46     | 2.83 ± 0.45            | 2.69 ± 0.44              | 2.69 ± 0.46                 | 2.48 ± 0.46                | 0.049   |
| ES wall stress index           | 0.99 ± 0.24     | 1.07 ± 0.23            | 0.93 ± 0.16*             | 0.96 ± 0.25*                | 0.83 ± 0.25*               | <0.001  |
| Peak systolic wall stress, N/m² | 15.7 ± 3.6     | 16.0 ± 3.5             | 14.1 ± 2.0               | 16.6 ± 3.9*                 | 14.2 ± 3.8                 | 0.005   |
| Area strain, %                 | 69 ± 11         | 66 ± 10                | 71 ± 8                   | 69 ± 12                     | 79 ± 13**                  | <0.001  |

Table 1. Baseline demographics, clinical and left ventricular parameters for all subjects and by age groups. Data were represented as mean ± SD or percentage. SBP: systolic blood pressure; DBP: diastolic blood pressure; LV: left ventricle; ED: end-diastolic; ES: end-systolic; EDV: end-diastolic volume; ESV: end-systolic volume. P value is from one-way analysis of variance (ANOVA) across the four age groups with Bonferroni test, a P value of 0.05 was considered significant. *Significant difference compared to Young group; †significant difference compared to Mid-age group; ‡significant difference compared to Young-Old group.

gender stratified by age group. Only in the ≤44 years group did females have significantly higher CED and WS than males. Except for the 75–84 years group, females had significantly smaller WTD and WTES and larger σs in the other three age groups. Increased AS was observed in females for the ≤44 and 45–64 years groups (P < 0.05). Age × gender interactions were non-significant for all parameters, indicating relative constancy in differences between males and females across age categories. No significant differences were detected among age categories with respect to WTD (P = 0.626) and WTES (P = 0.133), indicating no significant effect of age on wall thickness. Significant differences in σs were observed among the four age groups (P = 0.0051), while associations with age (P = 0.348) and gender differences (P = 0.808) were non-significant. Plotted in Figure S are linear regressions of CED, CWS, WTD, WTES, σED, σES and AS vs age stratified by gender showing 95% confidence intervals and prediction intervals.

Associations of age and gender with 3D regional parameters. We also investigated associations of age and gender vs LV function and 3D regional parameters, and the correlation coefficients are given in Table 4. Significant negative association with age was observed for both males and females for LV EDV index and LV ESV index, while LV EF was positively associated with age (P < 0.05 for both genders). However, only females had significant positive association with age for LV mass-to-volume ratio (r = 0.453, P < 0.01). Correlation of CED with age was higher for males than females (r = 0.271, P < 0.05 vs r = 0.142, P = NS), while negative association of σs with age was more pronounced in females than in males (r = −0.363 vs r = −0.285, both P < 0.01). Correlation between wall thickness and age was higher in females vs. males at both ED (r = 0.313, P < 0.01 vs r = −0.085,
Table 2. Comparison of demographics and 3D regional parameters by gender. Data were represented as mean ± SD. LV: left ventricle; ED: end-diastolic; ES: end-systolic. P value is from two-sample independent T-test.

| Parameters                          | Male (n = 83) | Female (n = 88) | P Value |
|-------------------------------------|---------------|-----------------|---------|
| Age, years                          | 53 ± 19       | 50 ± 19         | 0.297   |
| Height, cm                          | 169 ± 7       | 157 ± 6         | <0.001  |
| Weight, kg                          | 67 ± 12       | 56 ± 10         | <0.001  |
| Body surface area, m²               | 1.77 ± 0.19   | 1.55 ± 0.15     | <0.001  |
| Body mass index, kg/m²              | 23.5 ± 3.2    | 22.4 ± 3.2      | 0.026   |
| Systolic blood pressure, mmHg       | 140 ± 18      | 130 ± 21        | 0.001   |
| Diastolic blood pressure, mmHg      | 81 ± 9        | 73 ± 10         | <0.001  |
| Heart rate, bpm                     | 77 ± 12       | 76 ± 12         | 0.423   |
| LV end-diastolic volume index, ml/m³ | 71 ± 12       | 67 ± 10         | 0.013   |
| LV end-systolic volume index, ml/m³ | 26 ± 7        | 24 ± 7          | 0.031   |
| LV stroke volume index, ml/m³       | 45 ± 7        | 43 ± 6          | 0.058   |
| LV ejection fraction, %             | 63 ± 6        | 64 ± 6          | 0.414   |
| LV mass index, g/m²                 | 51 ± 10       | 39 ± 7          | <0.001  |
| LV mass-to-volume ratio, g/ml       | 0.72 ± 0.16   | 0.59 ± 0.12     | <0.001  |
| ED curvature (CED), mm⁻¹             | 0.039 ± 0.004 | 0.042 ± 0.004   | <0.001  |
| ES curvature (CES), mm⁻¹             | 0.066 ± 0.011 | 0.071 ± 0.010   | 0.003   |
| ED wall thickness (WTED), mm         | 5.33 ± 0.61   | 4.53 ± 0.70     | <0.001  |
| ES wall thickness (WTES), mm         | 8.20 ± 1.07   | 7.33 ± 1.21     | <0.001  |
| ED wall stress index (σED), %        | 2.55 ± 0.38   | 2.89 ± 0.47     | <0.001  |
| ES wall stress index (σES), %        | 0.96 ± 0.23   | 1.01 ± 0.24     | 0.114   |
| Peak systolic wall stress (σp), 1000 N/m² | 15.8 ± 3.7 | 15.6 ± 3.5     | 0.670   |
| Area strain (AS), %                 | 67 ± 11       | 72 ± 11         | 0.001   |

P = NS and ES (r = 0.331, P < 0.01 vs r = 0.092, P = NS). No significant correlation was observed between σED and age in either males or females (r = −0.104 vs r = −0.047, both P = NS). For AS, males were more correlated with age than females (r = 0.362 vs r = 0.284, both P < 0.01).

Intra- and inter-observer agreement. Table 5 shows the intra- and inter-observer variability for CED, CES, WTED, WTES, AS, σED, σES and AS, respectively. Intra-observer intraclass correlation coefficient (ICC) and coefficient of variation (CV) were 0.949–0.993 and 3.3–8.8%, and inter-observer ICC and CV were 0.924–0.991 and 3.9–10.1%. Both intra- and inter-observer variability have small biases and limits of agreement.

Discussion

Our study establishes the age- and gender-specific CMR reference ranges for 3D regional LV curvedness, thickness, wall stress index and area strain that can be automatically calculated from the reconstructed LV geometry. Age was positively associated with curvedness and area strain more in males, while negatively correlated with wall thickness. Intra-observer action effects were non-significant for all parameters. Regional parameters derived from the reconstructed LV geometry can provide new insights into the local mechanics that are not apparent from the 2D approach. Transthoracic echocardiography (TTE) is the standard commonest clinical imaging modality for measuring LV wall thickness at the ED phase from the left parasternal long-axis view, but is highly dependent on imaging plane obliquity, acoustic window and operator. In Hindieh, et al., discordant measurements between TTE and CMR in maximal LV wall thickness at the parasternal long- and short-axis views were present in a significant subset of HCM patients because of TTE technique limitations. CMR has been shown to be superior to TTE in measuring LV chamber dimensions and wall thickness owing to image quality and accuracy with better reproducibility than TTE. CMR 2D normal values for ED wall thickness were established from 300 participants (ages 45–94) free of cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, and measurements were performed on both cine short- and long-axis images using QMass V.7.2 (Medis Medical Imaging Systems, Netherlands). Compared with their results, our wall thickness values tended to be smaller. The discrepancy can be explained by: (1) LV wall thickness increases with aging, and participants in their paper were middle-aged or older compared with our relatively younger cohort (mean age 66 ± 9 years vs 52 ± 19 years, respectively); (2) participants in the MESA study had larger LV mass index (and thereby thicker LV myocardial wall) on average compared with our Asian cohort (85.1 ± 15.2 vs 51 ± 10 g/m² in males and 66.9 ± 10.9 vs 39 ± 7 g/m² in females); and 3) variations in measurement methodology. In our study, wall thickness was computed from a 3D reconstructed LV model and is the mean of the wall thicknesses of all points within the segment. The wall thickness is defined as the length of a ray with origin at a point of interest on the endocardial surface that is directed towards, and terminates at its intersection with the epicardial surface, and is neither dependent on the location of a center point nor imaging frame of reference.
This ray is not in the same plane as, and is always shorter than the distance measured on, standard 2D short- and long-axis slices. It approximates the “true” wall thickness in 3D space, and unlike 2D measurements, is independent of inaccuracies in slice positioning. Therefore, as suggested by Kawel, et al., it is critical to report the measurement technique along with the measured parameters. In addition, from the 16 segment plots in Figure 3, larger values of wall thickness are seen in segments containing the interventricular septum (IVS) in both males and females, indicating an asymmetry of LV myocardium that is similarly seen on 2D measurements.

2D curvature has been proposed for characterizing LV local shapes in different HCM subtypes using independent coordinates method. In pulmonary hypertension patients, the ratio of IVS curvature and free wall curvature at the ES phase by the three-point arc method was used to predict right ventricular (RV) systolic...
Several shape descriptors have been proposed to characterize and quantify the differential properties of surfaces. The most common ones —first mentioned by Koenderink and Van Doorn— are Gaussian curvature ($K = k_1 k_2$), mean curvature ($H = (k_1 + k_2)/2$) and curvedness ($C = \sqrt{k_1^2 + k_2^2}/2$). Mean curvature $H$ measured...
on 3D echocardiography (3DE) has been proposed by Addetia, et al., to discriminate normal pressure from right ventricular pressure overload in pulmonary arterial hypertension patients, and normal 3DE values of RV regional curvature indices were established by the same group. In a retrospective study of 416 inpatients using 2DE and 3DE, regional curvature provided additional mortality risk prediction beyond global longitudinal strain and LV EF. A serious limitation of curvature analysis is that the curvature will be zero at the saddle point even when the surface is curved. Similarly, Gaussian curvature is zero at the parabolic line on a toroidal surface even as the surface is curved.

Figure 3. Regional segment comparison between male and female for regional parameters. Curvedness at ED and ES (first row), wall thickness at ED and ES (second row), wall stress index at ED and ES (third row), peak systolic wall stress (last row, left) and area strain (last row, right). ED: end-diastole; ES: end-systole. * denotes significant difference with \( P < 0.05 \) (colors of * correspond to segment colors if points overlap).
Table 3. Summary of results from statistical analysis on 3D regional parameters by age category, mean (SD).
SD: standard deviation; ANOVA: analysis of variance; ED: end-diastolic; ES: end-systolic; LS: least squares; LT: linear trend. *significant difference between male and female, bolded text indicates a significant P value.

| Parameters | Gender | Age category (years) | Mean (SD) | Gender | P Value |
|------------|--------|----------------------|-----------|--------|---------|
| ED curvedness (C_{ED}), mm^-1 | M | <44 (Young) (n = 66, M/F 30/36) | 0.038 (0.004) | 0.040 (0.005) | 0.039 (0.004) | 0.042 (0.002) | 0.04 | A: 0.0460 |
| | F | 0.042 (0.004)* | 0.041 (0.003) | 0.042 (0.004) | 0.0044 (0.003) | 0.042 | I: 0.4315 |
| | Pooled | 0.04 | 0.041 | 0.04 | 0.043 | | LT: 0.0067 |
| ES curvedness (C_{ES}), mm^-1 | M | <44 (Young) (n = 66, M/F 30/36) | 0.062 (0.010) | 0.066 (0.009) | 0.066 (0.013) | 0.075 (0.009) | 0.068 | A: 0.0011 |
| | F | 0.070 (0.010)* | 0.070 (0.008) | 0.069 (0.009) | 0.081 (0.014) | 0.073 | I: 0.7227 |
| | Pooled | 0.066 | 0.068 | 0.068 | 0.078 | | LT: 0.0001 |
| ED wall thickness (WT_{ED}), mm | M | <44 (Young) (n = 66, M/F 30/36) | 5.37 (0.50) | 5.34 (0.43) | 5.32 (0.79) | 5.13 (0.65) | 5.29 | A: 0.6258 |
| | F | 4.34 (0.66)* | 4.62 (0.66)* | 4.65 (0.66)* | 4.90 (0.97) | 4.62 | I: 0.1605 |
| | Pooled | 4.85 | 4.98 | 4.99 | 5.01 | | LT: 0.4127 |
| ES wall thickness (WT_{ES}), mm | M | <44 (Young) (n = 66, M/F 30/36) | 8.09 (0.92) | 8.24 (0.54) | 8.34 (1.40) | 8.02 (1.14) | 8.17 | A: 0.1325 |
| | F | 6.94 (1.16)* | 7.62 (1.06)* | 7.43 (1.10)* | 8.13 (1.75) | 7.53 | I: 0.2596 |
| | Pooled | 7.51 | 7.93 | 7.89 | 8.07 | | LT: 0.1110 |
| ED wall stress index (σ_{ED}), kPa | M | <44 (Young) (n = 66, M/F 30/36) | 2.61 (0.36) | 2.47 (0.30) | 2.55 (0.45) | 2.43 (0.29) | 2.52 | A: 0.0479 |
| | F | 3.01 (0.44)* | 2.85 (0.47)* | 2.85 (0.44)* | 2.53 (0.62) | 2.81 | I: 0.6604 |
| | Pooled | 2.81 | 2.66 | 2.7 | 2.48 | | LT: 0.0160 |
| ES wall stress index (σ_{ES}), kPa | M | <44 (Young) (n = 66, M/F 30/36) | 1.04 (0.24) | 0.90 (0.10) | 0.93 (0.27) | 0.84 (0.17) | 0.93 | A: 0.0004 |
| | F | 1.10 (0.23) | 0.94 (0.20) | 1.00 (0.21) | 0.82 (0.33) | 0.97 | I: 0.9206 |
| | Pooled | 1.07 | 0.92 | 0.96 | 0.83 | | LT: 0.0011 |
| Peak systolic wall stress (σ_{p}), 1000 N/m² | M | <44 (Young) (n = 66, M/F 30/36) | 16.4 (3.8) | 14.2 (1.8) | 16.3 (4.1) | 14.4 (2.5) | 15.3 | A: 0.0051 |
| | F | 15.7 (3.3) | 13.9 (2.2) | 16.9 (3.5) | 14.1 (5.0) | 15.2 | I: 0.7890 |
| | Pooled | 16.1 | 14.1 | 16.6 | 14.2 | | LT: 0.3482 |
| Area strain (AS), % | M | <44 (Young) (n = 66, M/F 30/36) | 63 (9) | 66 (6) | 69 (12) | 74 (11) | 68 | A: 0.0002 |
| | F | 69 (10)* | 74 (7)* | 70 (10) | 84 (14) | 74 | I: 0.3250 |
| | Pooled | 66 | 67 | 67 | 74 | | LT: 0.00169 |

In contrast, point curvedness is zero only when the surface is flat, and varies monotonically with the magnitude of surface curve characteristics. In Maffessanti, et al., curvedness, normalized to instantaneous LV size, was calculated using prototype software (4D-LV Analysis MR, TomTec Imaging Systems, Unterschleissheim, Germany) and compared between segments for subjects with normal LV function (n = 14), dilated cardiomyopathy (n = 15) and ischemic heart failure (n = 15) using CMR images. The study size does not permit the determination of normal ranges of curvedness parameters. In contrast, our study, which recruited equal proportions of healthy male and female subjects stratified by age, is sizeable and able to establish gender- and age-specific normal ranges. Our results show that curvedness at ES is positively associated with age, indicating that the endocardial surface at the ES phase becomes more spherical during the ageing process.

LV wall stress is proportional to wall radius and inversely proportionate to wall thickness according to Laplace’s law. Numerous formulas have been proposed to evaluate wall stress that assume the LV as an ideal spherical, spheroidal or ellipsoidal shape. Some of these geometrical limitations can be overcome by finite approaches involving surface area parameters.
element analysis (FEA) which is a numerical and engineering technique for solving complicated structural problems. The characteristics of wall stress have been applied in translational research to analyze LV mechanics\textsuperscript{26,27}. From the curvature-based wall stress index formula, increases in curvedness and wall thickness with ageing (decrease of radius-to-thickness ratio $R/WT$) will contribute to decreases in wall stress index, which is what we show in Table 4 ($r = -0.213$ for $\sigma_{i,ED}$ and $r = -0.331$ for $\sigma_{i,ES}$). However, for peak systolic wall stress $\sigma_{ES}$, which incorporates systolic blood pressure into the ES wall stress index, no association with age was found. Across each age group, $\sigma_{ES}$ first decreased in the 45–64 years age group due to the decrease in radius-to-thickness ratio, then...
increased in the 65–74 years group because $R/WT$ is counterbalancing the somewhat elevated systolic blood pressure. Even though there was no clinical history of hypertension in the study population, $\sigma_{ES}$ eventually dropped in the 75–84 years group. However, $\sigma_{ES}$ exhibited no significant differences between males and females for all subjects, which implies that $\sigma_{ES}$ can be thought of as an intrinsic contractility index that is independent of gender that can potentially be helpful for longitudinal and/or therapeutic monitoring in disease applications.
studies used percentage change in area from the original dimensions to quantify AS28,29. In contrast, our cal-
regional changes from the circumferential, longitudinal and radial directions. Previous 3D echocardiography
groups —HF with reduced EF (HFrEF, EF ≤ mid-range EF (HFmrEF, 40% < EF ≤ 50%); n = 10, 7 males, mean age 59 ± 13 years, range = 38–75 years) and preserved EF (HFpEF, EF ≥ 50%; n = 10, 8 males, mean age 58 ± 14 years, range = 37–77 years)— were evaluated using the 3D regional analysis described in this study. Comparisons of demographics and regional parameters in each group against the normal reference values are presented in Table 6. For LV volume indices, LVEF, LV mass index and all regional parameters, there were significant differences among Controls and the three HF patient groups (all P ≤ 0.008). Both ED and ES curvedness in the HF patient groups were smaller than in the normal references and decreased from HFpEF to HFmrEF to HFrEF, implying that the LV was becoming flatter with decrease in LV EF. LV myocardial wall was thicker in HF patient groups than normal group, and ES wall thickness increased from Control to HFmrEF to HFrEF to HFpEF. With the progressive reduction of EF, HF patients had a propensity for higher wall stress index at ES and peak systolic wall stress, with trend HFpEF to Control to HFmrEF to HFrEF. The HFrEF stress was about twice that in Controls and around 2.7 times that in

| Parameters                              | All subjects (n = 171) | Male (n = 83) | Female (n = 88) |
|-----------------------------------------|------------------------|---------------|-----------------|
| LV end-diastolic (ED) volume index, ml/m² | -0.408**               | -0.438**      | -0.433**        |
| LV end-systolic (ES) volume index, ml/m² | -0.404**               | -0.413**      | -0.443**        |
| LV ejection fraction, %                 | 0.255**                | 0.232**       | 0.291**         |
| LV mass index, g/m²                     | -0.013                 | -0.234*       | 0.147           |
| LV mass-to-volume ratio, g/ml           | 0.267**                | 0.108         | 0.453**         |
| ED curvedness (C_ED), mm⁻¹              | 0.089                  | 0.217*        | 0.014           |
| ES curvedness (C_ES), mm⁻¹              | 0.184*                 | 0.271*        | 0.142           |
| ED wall thickness (WT ED), mm           | 0.151*                 | -0.085        | 0.313**         |
| ES wall thickness (WT ES), mm           | 0.233**                | 0.092         | 0.331**         |
| ED wall stress index (σ ED), mm⁻¹       | -0.213**               | -0.088        | -0.286**        |
| ES wall stress index (σ ES), mm⁻¹       | -0.331**               | -0.285**      | -0.363**        |
| Peak systolic wall stress (σ ES), 1000 N/m² | -0.073                 | -0.104        | -0.047          |
| Area strain (AS), %                     | 0.293**                | 0.362**       | 0.284**         |

Table 4. Correlation of age with left ventricular (LV) function measurements and 3D regional parameters. *Correlation significant at the 0.05 level; **correlation significant at the 0.01 level.

| Parameters                              | Intra-observer (n = 20) | Inter-observer (n = 20) |
|-----------------------------------------|-------------------------|-------------------------|
|                                          | ICC                     | Bias (limits of agreement) | CV, % | ICC                     | Bias (limits of agreement) | CV, % |
| ED curvedness (C_ED), mm⁻¹              | 0.993                   | 0.0007 (−0.0027, 0.0040) | 3.3   | 0.991                   | 0.0011 (−0.0026, 0.0047) | 3.9   |
| ES curvedness (C_ES), mm⁻¹              | 0.988                   | −0.0020 (−0.0101, 0.0142) | 6.7   | 0.985                   | −0.0021 (−0.0112, 0.0157) | 7.5   |
| ED wall thickness (WT ED), mm           | 0.981                   | 0.02 (−0.74, 0.78)       | 4.9   | 0.976                   | 0.16 (−0.70, 1.01)        | 5.9   |
| ES wall thickness (WT ES), mm           | 0.985                   | 0.01 (−1.10, 1.11)       | 4.5   | 0.969                   | 0.06 (−1.50, 1.62)        | 6.3   |
| ED wall stress index (σ ED), mm⁻¹       | 0.952                   | −0.03 (−0.49, 0.43)      | 7.0   | 0.955                   | −0.12 (−0.57, 0.33)       | 7.6   |
| ES wall stress index (σ ES), mm⁻¹       | 0.949                   | 0.02 (−0.74, 0.78)       | 8.5   | 0.924                   | −0.02 (−0.24, 0.21)       | 10.1  |
| Peak systolic wall stress (σ ES), 1000 N/m² | 0.951                 | −0.24 (−3.53, 3.05)     | 8.8   | 0.931                   | −0.27 (−4.02, 3.49)       | 10.0  |
| Area strain (AS), %                     | 0.989                   | 0.01 (−0.06, 0.09)       | 3.8   | 0.980                   | 0.01 (−0.09, 0.11)        | 5.0   |

Table 5. Intra- and inter-observer reproducibility of 3D regional parameters. ED: end-diastole; ES: end-systole; ICC: intraclass correlation coefficient; CV: coefficient of variation.

Area strain AS reflects endocardial surface deformation during contraction and relaxation and integrates the regional changes from the circumferential, longitudinal and radial directions. Previous 3D echocardiography studies used percentage change in area from the original dimensions to quantify AS28,29. In contrast, our calculation was based on the natural log (ln) function of the ratio of surface area at ES and ED1. We found a significant gender difference in AS with greater deformation magnitude in females and greater rates of increase with age in males (r = 0.362). A similar trend was found for peak systolic longitudinal strain evaluated by CMR feature-tracking (CMR FT)30, an emerging technique for quantitating myocardial deformation in both clinical and research settings. Normal strain ranges using this approach have been presented1,30–32, however, only 2D basal, mid-cavity and apical LV short-axis slices were used to calculate global circumferential and radial strains, and only three standard LV long-axis views for global longitudinal strain. Hyperelastic warping is another technique employed to characterize cardiac motion and function measurement in finite deformation continuum mechanics and image-based data33, and this method has been applied to characterizing pulmonary hypertension34–36 and heart failure with preserved ejection fraction37. Strain measurements from this technique are based on the reconstruction of a 3D biventricular model that can extract circumferential, longitudinal and radial strains for the LV, RV and septum simultaneously.

To demonstrate the clinical utility of normal reference values for curvature-based LV parameters, three patient groups —HF with reduced EF (HFrEF, EF < 40%; n = 10, 7 males, mean age 57 ± 11 years, range = 35–76 years); mid-range EF (HFmrEF, 40% ≤ EF < 50%; n = 10, 7 males, mean age 59 ± 13 years, range = 38–75 years) and preserved EF (HFpEF, EF ≥ 50%; n = 10, 8 males, mean age 58 ± 14 years, range = 37–77 years)— were evaluated using the 3D regional analysis described in this study. Comparisons of demographics and regional parameters in each group against the normal reference values are presented in Table 6.
HFpEF. This can be explained as follows: the normal or near normal chamber size and increased wall thickness relative to chamber dimension in HFpEF patients (concentric remodeling) resulted in reduced wall stress relative to Control. In contrast, in HFrEF, there is LV chamber dilatation (eccentric remodeling), with increase in LV radius. However, the decrease of AS was from Control to HP, E to HFrEF to HFpEF. Moreover, HFrEF and HFpEF were significantly different from Control, HFpEF and each other. The bar graphs in Figure 6 present aggregated values at the basal, mid and apical levels observed in Control (blue bars) and the three HF groups (HFpEF: cyan bars; HFrEF: yellow bars; HFpEF: dark red bars) with curvedness (first row) at ED and ES (left and right, respectively), wall thickness (second row) at ED and ES, wall stress index (third row) at ED and ES, and peak systolic wall stress (last row, left) and area strain (last row, right). Special attention should be paid to the three wall stress parameters: in Control, the mid-level had the largest values whereas in the three HF patient groups, the largest values occurred at the apical level.

These reference values were derived from a multi-ethnic Singaporean cohort with predominant Chinese ethnicity, which may limit the generalizability of the indices to Western populations. Our group has previously demonstrated that standard CMR parameters like chamber volumes and mass derived from a predominantly Chinese population were different than Western norms. As such, it would not be surprising if reference ranges for curvedness-based parameters were to differ between ethnic groups. Fortunately, curvedness and the derived parameters can be determined expeditiously with post-processing of standard cine CMR images, and can therefore be applied retrospectively to extant research or clinical image repositories to generate reference ranges in different populations and/or diverse disease states.

The sample size in the 75–84 years group was smaller than the other age groups owing to challenges in recruiting older subjects free of cardiovascular diseases, hypertension, diabetes and dyslipidemia. In the present study, manual delineation of endocardial and epicardial contours at ED and ES was needed to generate inputs for 3D geometric reconstruction, which is manually intensive. Incorporation of automatic segmentation and deep learning techniques may reduce processing time, is the next logic step. One of the limitations in our current reconstruction approach is the omission of the true apex (Segment 17 on the standard nomenclature) as it cannot be easily identified using the short-axis images due to thick (10 mm) slice acquisition. This may potentially lead to underestimation of LV volume. Another limitation concerns the tracking of LV chamber height, which shortens from ED to ES. LV chamber height is measured using the line joining the LV apex to the midpoint of the straight line connecting the two atrioventricular junctions, which assumes that the base of the LV is a flat plane orthogonal to the image defined solely by the two atrioventricular junction points. In reality, the LV basal surface is non-planar and the mitral valve is saddle-shaped. In our study, endocardial and epicardial borders at the base of the LV were manually contoured on short-axis cine CMR images, which is the routine in research and clinical laboratories. The left atrium (LA)-LV and LV-Aorta (AO) intersections are almost tangential to, and frequently not well-defined on, LV short-axis planes. A more optimal approach would be to reconstruct a whole heart model with the left atrium (LA) and aorta (AO) intact, and then to subsequently isolate the LV by truncating at the mitral annular and aortic planes. In a prior work, we acquired a series of 18 rotational slices at 10° angular equidistance in the LV long axis—the line extending from the LV apex to the center of mitral valve orifice—that depicts the mitral valve and annulus comprehensively. Future work will be to develop an algorithm to construct a composite 3D LV+LA+AO geometric model using 18 rotational slices as the reference, and to compare volumetric measurements with the LV models reconstructed from routine CMR images.

One attractive feature of our CardioWerkz software is that it does not require additional image acquisition and only uses short- and long-axis CMR images acquired in routine clinical practice. The short-axis contours used for LV function measurements can be directly imported into CardioWerkz for LV regional parameter evaluation permitting retrospective study of various cohorts. The relatively complex structure of the RV has rendered it less studied compared with the LV. Normal values of RV regional curvature indices using 3D echocardiography have been established by Addetia, et al. However, acquisition of 3D RV echocardiographic data sets is quite challenging and often hampered by varying degrees of anterior wall dropout. Using routine CMR to reconstruct 3D RV geometry and performing curvedness analysis has been reported in our prior study. A future study will establish normal ranges of RV regional deformation using the same stacks of LV short-axis cine CMR images, which also cover the RV chamber, combined with automatic segmentation of RV endocardial contours.

We have established normal values for 3D regional curvedness, wall thickness, wall stress index and AS for healthy subjects across a broad age spectrum, and investigated the associations with age and gender. Our approach is highly reproducible and automatic apart from contour extraction. The parameters in this study may shed light on the LV regional deformation with ageing.

Methods

Study population. Between July 2011 and July 2016, 444 healthy asymptomatic subjects (age range 20–87) without known cardiovascular disease were recruited from the community to undergo CMR. Those with prior history of hypertension, dyslipidemia, diabetes mellitus, and detected to have LV ejection fraction (EF) < 50% on CMR were excluded from analysis, leaving a final study sample of 171 subjects. The study was conducted in accordance with the Declaration of Helsinki and approved by the SingHealth Centralized Institutional Review Board. Written informed consent was obtained from all subjects.

As a clinical application of our normal ranges, we also included three heart failure (HF) patient groups — HF with reduced EF (HFrEF, EF < 40%; M/F: 7/3); mid-range EF (HFrEF, 40% ≤ EF < 50%; M/F: 7/3) and preserved EF (HFrEF, EF ≥ 50%; M/F: 8/2). Inclusion criteria of HF required the presence of signs or symptoms of HF based on modified Framingham criteria and prior hospitalization with primary diagnosis of HF. Exclusion criteria for HF included specific subgroups of HF (e.g., amyloidosis, eosinophilic myocarditis, etc.) and isolated right heart disease.
publications5,7. The LV endocardial mesh is then partitioned into 16 segments (excluding the true apex, which

Figure 1. The key steps are: correction of any misalignment in the LV short-axis slices arising from patient motion
to reconstruct the 3D LV geometry. CardioWerkz is a proprietary in-house developed software comprising a
LV short-axis images from QMass were imported into our in-house software (CardioWerkz, version 0.9 beta)
morphing approach51. Details of the reconstruction approach and methodology can be found in our previous

correction where needed.
contours in the remaining time phases were automatically tracked for each short-axis slice and manually cor-

reconstruction parameters is illustrated in
suite of algorithms for geometrical reconstruction of the left heart and its subsequent analysis. The workflow for

Calculation of 3D LV regional parameters. Curvedness (C) measures the degree of curvature at a given point, and how it deviates from flatness on a surface. It was calculated using the formula\(^5,16\)
Figure 6. Bar chart comparison of aggregated means at basal, mid and apical levels between Control (n=171), HFpEF (n=10), HFmrEF (n=10) and HFrEF (n=10) groups. First row: curvedness at ED (left) and ES (right), second row: wall thickness at ED (left) and ES (right), third row: wall stress index at ED (left) and ES (right), last row: peak systolic wall stress (left) and area strain (right). HF: heart failure; EF: ejection fraction; HFpEF: HF with preserved EF; HFmrEF: HF with mid-range EF; HFrEF: HF with reduced EF; ED: end-diastole; ES: end-systole. *Significant difference compared to Control; †significant difference compared to HFpEF; ‡significant difference compared to HFmrEF.
curvature-based wall stress index computed at ES by Eq. (2). The multiplier 0.133 expressed the final result in

\[ C = \sqrt{\frac{k_1^2 + k_2^2}{2}} \]  

(1)

where \( k_1 \) and \( k_2 \) are the maximum and minimum principal curvatures computed from the first and second fundamental form of the surface. LV wall thickness at ED (\( WT_{ED} \)) and ES (\( WT_{ES} \)) for each segment were calculated using a previously derived formula. Thick-walled elliptical and spherical models had been proposed for calculating pressure-normalized wall stress, obviating the need for invasive LV pressure measurement. In the current study, the curvature-based wall stress index \( \sigma_n \) was determined from the inner radius of curvature (\( R \)) and wall thickness \( WT \):

\[ \sigma_i = \frac{R}{2WT \left(1 + \frac{WT}{2R}\right)} \]  

(2)

Following Grossman et al., peak systolic wall stress (\( \sigma_{ES} \)) was calculated as

\[ \sigma_{ES} = 0.133 \times SP \times \sigma_{i,ES} \]  

(3)

where \( SP \) denotes peak systolic ventricular blood pressure (= 0.9 × systolic blood pressure) and \( \sigma_{i,ES} \) is the curvature-based wall stress index computed at ES by Eq. (2). The multiplier 0.133 expressed the final result in 1000 N/m².

Area strain is a quantitative strain measurement that incorporates endocardial wall strains in the circumferential, longitudinal and radial directions, and reflects the aggregate deformation of the LV endocardial surface with contraction and relaxation. The area strain (\( AS \)) was defined as

\[ AS = \ln \left( \frac{SA_{ES}}{SA_{ED}} \right) \times 100\% \]  

(4)

where \( SA_{ED} \) and \( SA_{ES} \) are endocardial surface areas at ED and ES phases, respectively.

Statistical analysis. Data assembly and statistical analysis were performed with SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA). All continuous variables were presented as mean ± standard deviation (SD). Associations between continuous variables were investigated using regression and correlation (Pearson). Comparisons of means between two independent groups were investigated using the two-sample t test. Comparison of means in three or more groups was investigated by one-way analysis of variance (ANOVA) with Bonferroni correction. Correlations of CMR measurements with gender and age were analyzed using a two-way analysis of variance model with factors age category (<44, 45–64, 65–74 and 75–84), gender (M/F), and age × gender interaction. F-tests were performed to test for significant differences in age category and gender main effect means, and for age × gender interaction effects.

Inter- and intra-observer reproducibility were assessed in 20 randomly chosen subjects via intraclass correlation coefficient (ICC), Bland-Altman analysis and coefficient of variation (CV). For inter-observer variability, LV endocardial and epicardial contours were segmented by a second independent observer (SL) blinded to the first observer’s results, and a second segmentation was made by the primary observer (XZ) one month after the initial segmentation to assess intra-observer variability. Statistical significance was set at \( P < 0.05 \).

Data availability
All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

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Author contributions
X.Z., S.K.T., L.Z., S.L., A.K., Y.S. and R.S.T. designed this work. A.K. and R.S.T. acquired the data for this work. X.Z., S.K.T., L.Z., Y.S. and R.S.T. analyzed and interpreted the work. X.Z., S.K.T., L.Z., S.L., J.M.Z., R.L., J.A., A.K., Y.S. and R.S.T. drafted the work and revised it critically for important intellectual content. All authors read and approved the final manuscript.

Competing interests
The authors declare no competing interests.

Additional information
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