Normative reference values for the tissue Doppler imaging parameters of left ventricular function: a population-based study

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Objective
Tissue Doppler imaging (TDI) is used routinely to quantify left ventricular function and filling pressure. However, there remains a lack of percentile-based normative reference values for these clinically important parameters.

Methods
Four hundred and fifty-three healthy subjects aged 35–75 years were included for analysis from the London Life Sciences Prospective Population (LOLIPOP) study. Subjects were free of manifest cardiovascular disease, cardiovascular risk factors, and significant coronary artery disease as determined by electron-beam computed tomography. They underwent 2D and Doppler echocardiography for assessment of left heart structure and function. TDI was performed at the septal and lateral mitral annular sites enabling on-line derivation of myocardial systolic velocity (Sa), diastolic velocity (Ea), and the ratio of Ea to transmitral E-wave (E/Ea).

Results
Reference ranges (5th and 95th percentile values) for septal, lateral, and average mitral annular Sa velocity, Ea velocity, and E/Ea ratio were derived for the whole cohort and for each of the four age groups (35–44, 45–54, 55–64, 65–75). Increasing age was associated with a significant attenuation in myocardial velocity when averaged from both the septal and lateral mitral annulus, exerting a greater influence upon average Ea velocity (P < 0.001) compared with average Sa velocity (P = 0.04). Average E/Ea ratio increased significantly with advancing age (P < 0.001).

Conclusion
The reference ranges presented for the TDI parameters of Sa velocity, Ea velocity, and E/Ea ratio will help to standardize the assessment of LV function by tissue Doppler echocardiography.

Keywords
Tissue Doppler • Reference values • Population study

Introduction
Tissue Doppler imaging (TDI) has emerged as one of the most powerful prognosticators for cardiovascular disease (CVD) within the realm of non-invasive cardiac imaging. The ability to quantify long-axis function of the myocardium in a reproducible manner has also significantly refined the assessment of left ventricular (LV) function. The TDI-derived parameters of myocardial systolic velocity (Sa), early diastolic velocity (Ea), and LV filling pressure (E/Ea) are used routinely in clinical echocardiography and they also underpin the recent European guidelines concerning the diagnosis of heart failure with normal ejection fraction (EF). The importance attached to these parameters has prompted attempts to derive their normative values. However, studies that have addressed this issue have tended to report average values for TDI parameters rather than standard deviation or percentile-derived reference ranges, which provide a more standardized and validated framework for partitioning echocardiographic variables.

Methodological heterogeneity in determining the myocardial time-velocity curve also exists. Myocardial velocities are usually...
obtained from the on-line, spectral pulsed tissue Doppler time-velocity curve in clinical practice, but for research purposes they can also be reconstructed off-line from colour-coded images superimposed on the 2D echocardiographic images. However, off-line reconstruction results in lower myocardial velocities than are achieved by on-line spectral analysis resulting in wide variation in published normative values. On-line assessment must be the technique of choice in the busy echo laboratory, and using this method, we describe reference ranges for normal Sa velocity, Ea velocity, and LV E/Ea. We studied subjects representing a biethnic, highly phenotyped cohort free of clinical CVD, traditional cardiovascular risk factors, and significant coronary artery disease.

**Methods**

Subjects were recruited between August 2004 and November 2007 from the LOLIPOP (London Life Sciences Prospective Population) study. LOLIPOP is an ongoing population-based study of ~30 000 Indian Asian and European white men and women recruited from the lists of 58 General Practitioners in West London. Assessment of participants was performed by a trained nurse using a standard protocol including questions on medical history, family history, cardiovascular risk factors, alcohol intake, physical activity, and drug history (verified from the practice computerized records). Subsequently, 2293 Indian Asian and European White subjects, aged 35–74 years and free from clinical CVD, were selected at random and enrolled into the LOLIPOP atherosclerosis cohort substudy.

Consenting subjects had a physical assessment including blood pressure (BP) determination, anthropometric measurements, and an electrocardiogram. Subjects were then invited to undergo echocardiography, electron-beam computed tomography (EBCT) for coronary calcium score determination (Agatston score) and provide fasting plasma and serum samples for biochemical analysis stored at −80 °C. The study was approved by the Northwick Park Hospital and Ealing Hospital Research Ethics Committees.

Echocardiograms were analysed in a subset of 453 healthy individuals having excluded subjects with either a coronary calcium score >10 Agatston units, or a prescription for cardioactive medications (anti-hypertensives, anti-arrhythmics, lipid lowering therapy, thienopyridine antiplatelets), or any traditional cardiovascular risk factors (systolic BP >140 mmHg, diastolic BP >90 mmHg, total cholesterol >6.0 mmol/L, fasting glucose >7.1 mmol/L, body mass index >30 kg/m², current smoking).

**Echocardiography**

**Left heart dimensions and ejection fraction**

Transthoracic 2D echocardiography was performed by experienced sonographers using a digital commercial harmonic imaging ultrasound system with an S3 3 MHz phased-array transducer (Philips IE33, Philips Medical Systems, Holland) at a single centre. LV dimensions were obtained in the parasternal short-axis view and LV mass was calculated using the Devereux formula and indexed to height to give LV mass index (LVMI). Quantitative 2D methods (biplane Simpson’s) were performed to obtain EF. Left atrial volume was calculated from three measurements of left atrial dimension using the formula for an ellipse and indexed to body surface area to obtain left atrial volume index (LAVI).

**Transmirtal flow and E/Ea ratio**

The transmirtal flow velocities were recorded using pulse-wave Doppler with the sample volume placed at the tip of the mitral valve leaflets in the apical 4-chamber view. From the mitral valve inflow velocity curve, the following measurements were made: peak E-wave velocity (cm/s); peak A-wave velocity (cm/s); and the ratio of E-wave to A-wave (E/A) velocities.

**Tissue Doppler imaging**

Myocardial velocities were measured on-line using a standard pulse-wave Doppler technique. Colour-coded images were acquired during a breath hold over two consecutive cardiac cycles using low-velocity, high-intensity myocardial signals at high frame rate (>150 MHz). The imaging angle was adjusted to ensure as near parallel alignment of the beam as possible with the myocardial segment of interest. The sample volume was placed at the junction of the LV wall with the mitral annulus of the septal and lateral myocardial segments in the apical 4-chamber view. Peak Sa and Ea velocities (cm/s) were measured on-line from both mitral annular site segments and the corresponding E-wave to Ea ratios calculated. Mean velocities and E/Ea ratios of the two mitral annular sites were then derived.

**Electron-beam computed tomography**

Coronary calcium imaging was performed using EBCT at a single centre with a modified GE Imatron C-150 (San Francisco, CA, USA) scanner specially equipped with high-resolution detectors. Scan time was 100 ms per slice, synchronized to 40% of the R–R interval. All areas of calcification within the borders of a coronary artery with an optical density >130 Hounsfield units and an area >1 mm² were computed. All calcium scores were calculated on an Aquarius workstation (TeraRecon, Inc., San Mateo, USA). The output from EBCT scans was quantified into Agatston scores.

**Statistical analysis**

Continuous variables are summarized as the mean ± 1 SD. Continuous variables and their association with age group were assessed using one-way analysis of variance and categorical data assessed by chi² test. Reference ranges for TDI parameters are presented as values denoting the 5th and 95th percentiles. The effect of age upon longitudinal function and LV filling pressure was assessed by Pearson’s correlation. Statistical analysis was performed using SPSS version 15 with values of P < 0.05 considered statistically significant.

**Interobserver variability**

Echocardiographic measurements were repeated by two sonographers in 15 subjects to assess reproducibility and interobserver variability. For mean Sa velocity, mean Ea velocity, and mean E/Ea ratio, the coefficient of variance was 11.4, 8.7, and 8.0%, respectively.

**Results**

Of the 2293 subjects recruited, 453 fulfilled the inclusion criteria for the purposes of this study. Their clinical characteristics stratified by age group are illustrated in Table 1. The mean age of the subjects was 51 years with 43% being of European white ethnicity and 56% of male gender. Systolic BP, pulse pressure, and total cholesterol both increased significantly with age, whereas there was no significant relationship between coronary calcium score and ageing. The cut-off for abnormal EF was 52% based on the 5th percentile value.
The E/A ratio decreased (P = 0.001), LVMI (P < 0.001), and EF (P = 0.004) all increased with advancing age. Age-specific and whole cohort averages with reference ranges (5th and 95th percentile) for Sa velocity, Ea velocity, and the E/Ea ratio are provided in Table 3. Myocardial Sa velocity measured at the septal mitral annulus was not significantly associated with age. However, Sa velocity measured at the lateral mitral annulus was significantly attenuated in the older subjects (P = 0.004). The average Sa velocity of the septal and lateral annuli also decreased with age (P = 0.04). The Ea velocity measured at both septal and lateral mitral annular segments, and their averages, decreased significantly with ageing resulting in a reciprocal and significant increase in the E/Ea ratio when measured at either annular site and when averaged between the two.

Figure 1 illustrates the relationship between age and the tissue Doppler parameters of LV function. Age was negatively correlated with both the longitudinal systolic and diastolic velocities, although the relationship was stronger with the latter (mean Sa velocity r = −0.14, mean Ea velocity r = −0.50). There was also a moderate, direct correlation between age and the E/Ea ratio (r = 0.30).

**Table 1** Demographics and clinical characteristics stratified by age

<table>
<thead>
<tr>
<th>Age</th>
<th>35–44</th>
<th>45–54</th>
<th>55–64</th>
<th>65–75</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>121</td>
<td>189</td>
<td>116</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>41 ± 2</td>
<td>50 ± 3</td>
<td>59 ± 3</td>
<td>69 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>54</td>
<td>60</td>
<td>47</td>
<td>67</td>
<td>0.07</td>
</tr>
<tr>
<td>European white (%)</td>
<td>36</td>
<td>44</td>
<td>47</td>
<td>53</td>
<td>0.24</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>114 ± 12</td>
<td>118 ± 11</td>
<td>120 ± 10</td>
<td>126 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>74 ± 7</td>
<td>76 ± 8</td>
<td>74 ± 7</td>
<td>74 ± 8</td>
<td>0.14</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>40 ± 8</td>
<td>43 ± 7</td>
<td>46 ± 8</td>
<td>52 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6 ± 0.2</td>
<td>24.8 ± 2.5</td>
<td>24.6 ± 2.9</td>
<td>25.5 ± 2.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.0 ± 0.8</td>
<td>5.2 ± 0.7</td>
<td>5.3 ± 0.7</td>
<td>5.2 ± 0.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Agatston score (Au)</td>
<td>0.2 ± 1.1</td>
<td>0.4 ± 1.4</td>
<td>0.4 ± 1.4</td>
<td>0.3 ± 0.8</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Continuous variables presented as mean ± SD. E, peak velocity of early filling; A, peak velocity of atrial filling; LAVI, left atrial volume index; LVMI, left ventricular mass index; ESVI, end-systolic volume index; EDVI, end-diastolic volume index; EF, ejection fraction.

**Table 2** Two-dimensional echocardiographic and Doppler data stratified by age

<table>
<thead>
<tr>
<th>Age</th>
<th>35–44</th>
<th>45–54</th>
<th>55–64</th>
<th>65–75</th>
<th>P-value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E (cm/s)</td>
<td>75.0 ± 15.3</td>
<td>72.5 ± 14.7</td>
<td>74.1 ± 16.7</td>
<td>64.7 ± 14.8</td>
<td>0.01</td>
</tr>
<tr>
<td>A (cm/s)</td>
<td>57.5 ± 12.4</td>
<td>63.1 ± 13.9</td>
<td>72.0 ± 17.9</td>
<td>71.8 ± 16.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.3 ± 0.3</td>
<td>1.2 ± 0.4</td>
<td>1.1 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAVI (mL/m²)</td>
<td>13.9 ± 4.5</td>
<td>14.9 ± 4.2</td>
<td>16.1 ± 4.6</td>
<td>16.7 ± 4.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVMI (g/m)</td>
<td>80.9 ± 20.5</td>
<td>84.3 ± 21.5</td>
<td>88.2 ± 23.6</td>
<td>97.4 ± 21.1</td>
<td>0.001</td>
</tr>
<tr>
<td>ESVI (mL/m²)</td>
<td>15.7 ± 4.7</td>
<td>15.0 ± 4.9</td>
<td>13.4 ± 4.3</td>
<td>15.0 ± 4.6</td>
<td>0.001</td>
</tr>
<tr>
<td>EDVI (mL/m²)</td>
<td>40.0 ± 10.4</td>
<td>40.0 ± 10.3</td>
<td>36.5 ± 9.9</td>
<td>38.7 ± 9.7</td>
<td>0.02</td>
</tr>
<tr>
<td>EF (%)</td>
<td>61 ± 5</td>
<td>63 ± 6</td>
<td>63 ± 6</td>
<td>62 ± 6</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD. E, peak velocity of early filling; A, peak velocity of atrial filling; LAVI, left atrial volume index; LVMI, left ventricular mass index; ESVI, end-systolic volume index; EDVI, end-diastolic volume index; EF, ejection fraction.

**Discussion**

In this study, we have presented age-specific normative reference values for the clinically important TDI parameters of LV function. These values are based on a large, biethnic cohort using strict criteria for normality to ensure that left ventricles of healthy subjects with low cardiovascular risk factor and coronary artery disease burden were studied. We have also confirmed the detrimental influence of natural ageing upon longitudinal myocardial function and LV filling pressure.

Several studies have attempted to derive normative values for TDI parameters but they have tended to explore the association of these parameters with age and have consequently reported only their mean values. Although a study by Munangala et al. described percentile-based reference ranges for the diastolic TDI parameters in a large population, reference values for myocardial Sa velocity were not reported. To the best of our knowledge, this is the first to study to have reported percentile-based partition values for both the systolic and diastolic TDI parameters of LV function.

Myocardial Sa velocity is an important and frequently overlooked component of systolic function that can be sensitively...
Table 3  Age-specific and whole-cohort reference ranges for Sa velocity, Ea velocity, and E/Ea ratio

<table>
<thead>
<tr>
<th>Age</th>
<th>Saseptal (cm/s)</th>
<th>Easeptal (cm/s)</th>
<th>Lateral annulus (cm/s)</th>
<th>Ealateral (cm/s)</th>
<th>E/Ealateral ratio</th>
<th>Ea ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>35–44</td>
<td>8.2 ± 1.6 (59–110)</td>
<td>9.5 ± 2.1 (61–113.3)</td>
<td>8.2 ± 2.1 (65–120)</td>
<td>5.5 ± 5.1 (5.5–120)</td>
<td>7.3 ± 2.1 (59–124.7)</td>
<td>6.9 ± 1.5 (45–97.2)</td>
</tr>
<tr>
<td>45–54</td>
<td>8.2 ± 1.6 (59–110)</td>
<td>9.5 ± 2.1 (61–113.3)</td>
<td>8.2 ± 2.1 (65–120)</td>
<td>5.5 ± 5.1 (5.5–120)</td>
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<tr>
<td>55–64</td>
<td>8.2 ± 1.6 (59–110)</td>
<td>9.5 ± 2.1 (61–113.3)</td>
<td>8.2 ± 2.1 (65–120)</td>
<td>5.5 ± 5.1 (5.5–120)</td>
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<td>6.9 ± 1.5 (45–97.2)</td>
</tr>
<tr>
<td>65–75</td>
<td>8.2 ± 1.6 (59–110)</td>
<td>9.5 ± 2.1 (61–113.3)</td>
<td>8.2 ± 2.1 (65–120)</td>
<td>5.5 ± 5.1 (5.5–120)</td>
<td>7.3 ± 2.1 (59–124.7)</td>
<td>6.9 ± 1.5 (45–97.2)</td>
</tr>
</tbody>
</table>

Abbreviations as used in Table 2 with Saseptal peak systolic septal mitral annular velocity; Easeptal peak early diastolic septal mitral annular velocity; Lateral annulus peak systolic lateral mitral annular velocity; Ea, peak early diastolic lateral mitral annular velocity. Values represent the mean ± SD and 5th–95th percentiles.

The influence of age upon myocardial function was more evident in the diastolic parameters measured, extending the findings of previous studies. A moderate, negative correlation was evident between Ea velocity measured at both the medial and lateral mitral annulus and age. The LV filling pressure, as estimated by E/Ea ratio, increased with normal ageing. The E/Ea ratio has been widely incorporated into clinical 2D echocardiography, offering a non-invasive technique of estimating LV filling pressure. TDI performed at the lateral mitral annulus yields higher longitudinal velocities hence a smaller E/Ea ratio than when derived from the septal site. Studies have varied with regard to which annular site the E/Ea ratio is measured from, and corresponding cut-off values have been proposed to optimally detect elevated LV filling pressure. However, guidelines for diagnosing diastolic heart failure are based on an average value of the two sites, with an average E/Ea > 15 deemed specific for elevated LV filling pressure and < 8 indicative of low/normal filling pressures. Intermediate values (8 < E/Ea < 15) are considered suggestive but not compelling evidence for elevated LV filling pressure, with the recommendation that ancillary, non-invasive investigations be performed to confirm or refute the diagnosis of heart failure. In this present study, upper limits of normal for E/Ea, defined as values representing the 95th percentile, exceeded 8 in all age groups even when averaged E/Ea ratios derived from both septal and lateral mitral annular sites were assessed. Our data do not support the assertion that intermediate E/Ea values may be indicative of elevated LV filling pressures as we observed that healthy subjects of any age were likely to have an E/Ea ratio exceeding 8 and frequently be > 10. An E/Ea ratio > 15 is, however, likely to represent abnormally elevated LV filling pressures regardless of age and the mitral annular site measured.
Increased LV mass is an independent risk factor for the development of heart failure, and in this cohort, we observed an age-related increase in LV mass, consistent with previous studies.22 – 24 The increase in LV mass is likely to be explained by the gradual increase in systolic BP that occurs with ageing,25 a relationship confirmed in this study. The intrinsic relationship between ageing and systolic BP resulting in increased LV mass is also the likely basis for the observation of attenuated myocardial function and augmented LV filling pressures with natural ageing. Left atrial size, a morphophysiological expression of LV filling pressure, was also observed to increase with age, again reflecting the progressive impairment of diastolic function that occurs due to an increasing LV mass.13

**Conclusion**

We have defined reference ranges for the TDI parameters of LV longitudinal function and filling pressure based on normative percentile values derived from a large population in whom the confounding effects of cardiovascular risk factor burden and significant CAD upon myocardial function have been largely obviated. These partition values should help in the standardization of clinical tissue Doppler echocardiography.

**Conflict of interest:** none declared.

**Funding**

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