Normal ranges for automatic measurements of tissue Doppler indices of mitral annular motion by echocardiography. Data from the HUNT3 Study

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Abstract

Background: Automatic quantification of left ventricular (LV) function could enhance workflow for cardiologists and assist inexperienced clinicians who perform focused cardiac ultrasound. We have developed an algorithm for automatic measurements of the mitral annular plane systolic excursion (MAPSE) and peak velocities in systole (S′) and early (e′) and late (a′) diastole. We aimed to establish normal reference values for the automatic measurements and to compare them with manual measurements.

Methods and Results: Healthy participants (n = 1157, 52.5% women) from the HUNT3 cross-sectional population study in Norway were included. The mean age ± standard deviation (SD) was 49 ± 14 (range: 19–89) years. The algorithm measured MAPSE, S′, e′, and a′ from apical 4-chamber color tissue Doppler imaging (cTDI) recordings. The manual measurements were obtained by two echocardiographers, who measured MAPSE by M-mode and the velocities by cTDI. For men and women, age-specific reference values were created for groups (mean ± 1.96SD) and by linear regression (mean, 95% prediction interval). Age was negatively correlated with MAPSE, S′, e′, and a′. There were small differences between genders. Normal reference ranges were created. The coefficients of variation between automatic and manual measurements ranged from 5.5% (S′) to 11.7% (MAPSE).

Conclusion: Normal reference values for automatic measurements of LV function indices are provided. The automatic measurements were in line with the manual measurements. Implementing automatic measurements and comparison with normal ranges in ultrasound scanners can allow for quick and precise interpretation of LV function.

Keywords: diastolic function, left ventricular function, mitral annular velocity, systolic function, ultrasound
1 | INTRODUCTION

Automatic analysis of echocardiograms is a rapidly evolving technology. Potential advantages include, but are not limited to, time-savings for cardiologists, reduced measurement variability, and assistance for less experienced users of both echocardiography and focused cardiac ultrasound.

We have developed an algorithm that automatically measures indices of left ventricular (LV) longitudinal function, namely the mitral annular plane systolic excursion (MAPSE) and the peak mitral annular velocities in systole (S′) and early (e′) and late (a′) diastole. The algorithm uses color tissue Doppler imaging (cTDI) echocardiographic recordings from high-end scanners. All the indices have shown prognostic value in heart failure. The automatic measurements have previously been shown to be in good agreement with measurements by experts and could be used to detect LV dysfunction. The algorithm can be implemented on hand-held ultrasound devices and high-end scanners for real-time automatic measurements.

To distinguish between normal and pathological measurements of a given echocardiographic index, normal reference values based on healthy populations are needed. Echocardiographic measurements can vary between different ultrasound scanner models, imaging modalities, and workstation software. Therefore, previously published reference values for manual measurements of mitral annular motion indices may not be optimal for interpretation of specific automatic measurements.

Mitral annular motion is influenced by age and gender. Indexing for body surface area has been suggested to be of less importance in recent studies. Most studies have published categorical reference values for men and women in age intervals of at least 10 years. Continuous reference values based on age could lead to more precise diagnostics.

Thus, we aimed to create age- and gender-specific reference values for automatic measurements of MAPSE, S′, e′, and a′ ready for easy implementation in the everyday clinic. We also aimed to validate the automatic measurements by comparing them to manual measurements.

2 | METHODS

2.1 | Study population

The third wave of the Nord-Trøndelag Health study (HUNT3) in Nord-Trøndelag County, Norway, was conducted from 2006 to 2008. Of 94,194 people invited, 50,839 (54.0%) were participated. The study included echocardiograms from 1,266 randomly selected volunteers, all free from known cardiovascular disease, hypertension and diabetes. For the purpose of this study, we excluded cases who had missing cTDI recordings, recordings with too much image noise for manual measurements, and cases where the automatic algorithm failed in tracking the mitral annulus correctly.

The study was approved by the Regional Committee for Medical Research Ethics and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2 | Image acquisition

All participants underwent a complete transthoracic echocardiographic examination that was conducted according to contemporary guidelines by one physician echocardiographer experienced in echocardiography. The acquisition protocol has been described previously. Shortly, participants were examined in the left-lateral decubitus position with a Vivid 7 scanner (version BT06) using a phased-array transducer (M3S with bandwidth 1.5–4.0 MHz or M4S with bandwidth 1.5–3.6 MHz) (GE Vingmed Ultrasound). From the apical 4-chamber projection, separate B-mode (grayscale) and cTDI recordings optimized for evaluation of the left ventricle were obtained. The grayscale recordings had a mean frame rate of 44 per second. The Doppler frames in the cTDI recordings had a mean frame rate of 100 per second, and the underlying grayscale images had a mean frame rate of 25 per second. Echocardiographic data were stored digitally and subsequently analyzed.

2.3 | Manual measurements of mitral annular motion indices

The recordings were analyzed by two experienced physician echocardiographers. Echocardiograms were analyzed for M-mode-derived MAPSE (Figure 1A) and cTDI-derived S′, e′, and a′ (Figure 1B) in two workstations from the same vendor (EchoPAC SWO, version 113 and 201, GE Vingmed Ultrasound). All measurements represented the average of three cardiac cycles.

Mitral annular plane systolic excursion was measured from the apical 4-chamber projection, either by standard M-mode or by reconstructed M-mode from two-dimensional (2D) grayscale recordings. The M-mode scan lines were aligned with the septal and lateral side of the mitral annulus near the insertion of the mitral leaflets. Septal and lateral measurements were averaged.

The apical 4-chamber cTDI recordings were analyzed for mitral annular velocities using the Q-analysis package in EchoPAC SWO. Circular regions of interest with diameter 5 mm were placed in the basal myocardium near the insertion of the mitral leaflets at the septal and lateral side. Septal and lateral measurements were averaged. The temporal smoothing of the velocity traces was set to 30 ms. The peak systolic velocity was set as the highest velocity observed during systole. The peak diastolic velocities were the minimum negative values during early and late diastole, both converted to absolute values.

2.4 | Automatic measurements of mitral annular motion indices

The apical 4-chamber cTDI recordings were transferred to a laptop computer, converted from DICOM (Digital Information and Communication in Medicine) to in-house file format and analyzed...
using the algorithm (Figure 1C). The mean computation time for analysis of each recording was 1.1 seconds. The method has been comprehensively described previously. Briefly, the measurements were acquired in three main steps: (a) Segmentation of the left ventricle on 2D grayscale frames, (b) cTDI-based tracking of the mitral annulus, and (c) analysis of cTDI-derived displacement and velocity curves. All automatic measurements were obtained from the septal and lateral side of the mitral annulus from three consecutive cardiac cycles and then averaged. All recordings were inspected to assess the mitral annular tracking. The tracking was judged as correct if the tracking points were located in the mitral annulus or basal myocardium near the insertions of the mitral valve leaflets for three consecutive heart cycles.

2.5 | Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Frequency variables are presented in absolute numbers and percentages. Distributions of continuous variables were assessed in histograms, and by evaluating skewness and kurtosis, where values of −2 to 2 for both were considered indicative of a normal distribution. Both automatic and manual measurements of the mitral annular motion indices were normally distributed (Figure 2). Linear correlations between continuous variables were assessed by Pearson’s correlation coefficient ($r$).

The study participants were stratified by gender and age (<40, 40–59 and ≥60 years). In each age group, the frequency of women and men in each age group was compared with the binomial test, and characteristics were compared with the independent $t$-test. The associations between (a) gender and age groups and (b) automatic measurements of mitral annular motion indices were tested by two-way analysis of variance, as all included cases had a complete set of measurements. Homogeneity of variances was evaluated by dividing the maximal variance by the minimal variance for each mitral annular motion index, where a ratio < 3 was considered to indicate homogeneity. For each index, homogeneity of variance was seen in all subgroups. $P$-values for differences in means between subgroups were Bonferroni-corrected.

Reference values based on gender and age groups were calculated as mean ± 1.96 SD, under the assumption that 95% of observations of a normally distributed variable can be expected to lie within such a range (prediction interval). The reference values for the gender-specific age groups are referred to as “categorical”. The
The association between age and the mitral annular motion indices was further assessed by regression analyses. Treating age as a continuous variable in linear regression, reference values were created by estimating means with 95% prediction intervals, under the assumption that 95% of individuals of a certain age will have mitral annular motion measurements within a corresponding prediction interval. These reference values are referred to as “continuous”.

The automatic and manual measurements were compared in Bland–Altman analyses and by calculating the coefficient of variation (CoV). The CoV was calculated as the within standard deviation of the difference between the automatic and manual measurements divided by the corresponding mean. Means of automatic and manual measurements were compared with a paired t-test. The 95% limits of agreement were calculated as mean difference ± 1.96 SD. All the statistical analyses were performed with SPSS version 25.0 (IBM Corp). P-values < .05 were considered statistically significant.

3 | RESULTS

3.1 | Study population

Among the 1266 cases available for inclusion, 5 (0.4%) were missing cTDI recordings, 6 (0.5%) had too much image noise for manual measurement acquisition, and 1 (0.1%) was excluded due to rocking myocardial motion. In the 1254 remaining cases, the algorithm could not read the cTDI recordings in 5 (0.4%), and the algorithm tracked the mitral annulus incorrectly in 92 (7.3%). Thus, 1157 cases of which 608 (52.5%) were women were included in the final analyses (Table 1). The mean age ± SD was 49 ± 14 years (range: 19–89 years). Although all were apparently healthy at study inclusion, 655 (56.6%) had body mass index > 25 kg/m² and 226 (19.5%) had systolic or diastolic blood pressure above 140 or 90 mm Hg, respectively.

3.2 | Relationship between gender, age and body surface area and the mitral annular motion indices

For the population as a whole, there was no significant difference in MAPSE between genders, but an interaction effect was found between gender and age groups (P < .001), where women had the largest differences in MAPSE between age groups. In both women and men, MAPSE was negatively correlated with age (r = −0.49, and −0.30, respectively, both P < .001). For the velocity indices, the relationship with age was similar for both genders. Women had lower S′ than men (6.6 ± 1.1 vs 6.9 ± 1.3 cm/s, P < .001). S′ was negatively correlated with age (r = −0.32, P < .001). Women had higher e′ than men (9.2 ± 2.5 vs 8.4 ± 2.5 cm/s, P = .009). There was a strong negative correlation between e′ and age (r = −0.74, P < .001). Women had lower a′ than men (7.6 ± 1.5 vs 8.0 ± 1.6 cm/s, P = .001), and a′ was positively correlated with age (r = 0.38, P < .001). For the study population as whole, body surface area was uncorrelated with MAPSE (r = 0.06, P = .054), slightly positively correlated with S′ (r = 0.11, P < .001) and a′ (r = 0.14, P < .001), and slightly negatively correlated with e′ (r = −0.10, P < .001).

3.3 | Reference values

Table 2 shows categorical reference values for automatic measurements according to gender and age groups. The categorical and
TABLE 1 Characteristics of the 1157 included participants

|                | <40 y |        |        | 40–59 y |        |        | ≥60 y |        |        |
|----------------|-------|--------|--------|---------|--------|--------|-------|--------|--------|
|                | Women | Men    | P      | Women   | Men    | P      | Women | Men    | P      |
| n              | 189   | 116    | <.001  | 309     | 299    | .72    | 110   | 134    | .14    |
| Age (years)    | 32.4 ± 6.0 | 32.2 ± 6.2 | .68    | 30.6 ± 6.0 | 49.3 ± 5.7 | .007  | 67.8 ± 5.7 | 68.5 ± 5.9 | .35    |
| Height (m)     | 1.67 ± 0.06 | 1.81 ± 0.06 | <.001  | 1.66 ± 0.06 | 1.79 ± 0.06 | <.001 | 1.63 ± 0.05 | 1.76 ± 0.06 | <.001  |
| Weight (kg)    | 71.4 ± 13.7 | 85.7 ± 13.2 | <.001  | 71.6 ± 11.6 | 86.6 ± 11.3 | <.001 | 69.7 ± 10.8 | 81.4 ± 10.2 | <.001  |
| BMI (kg/m²)    | 25.3 ± 4.4 | 26.1 ± 3.9 | .10    | 25.8 ± 3.9 | 26.8 ± 3.0 | .001  | 26.3 ± 3.8 | 26.2 ± 2.7 | .82    |
| BSA (m²)       | 1.80 ± 0.17 | 2.06 ± 0.16 | <.001  | 1.79 ± 0.15 | 2.06 ± 0.15 | <.001 | 1.74 ± 0.13 | 1.98 ± 0.14 | <.001  |
| Systolic BP (mm Hg) | 118.6 ± 11.6 | 127.5 ± 10.5 | <.001  | 125.9 ± 15.7 | 131.4 ± 12.4 | <.001 | 142.3 ± 19.7 | 138.4 ± 16.8 | .11    |
| Diastolic BP (mm Hg) | 68.2 ± 9.1 | 69.9 ± 9.4 | .12    | 71.7 ± 10.6 | 78.1 ± 9.4 | <.001  | 74.5 ± 10.2 | 77.0 ± 9.6 | .06    |

Note: Data are presented as mean ± standard deviation except for number of cases. Abbreviations: BMI = body mass index; BP = blood pressure; BSA = body surface area; n = number of cases; y = years.

Continuous reference values are interleaved in Figure 3 for comparison. The largest discrepancies between categorical and continuous reference values were seen for e’. Table 3 shows regression equations for the continuous reference values for automatic measurements. Categorical reference values and regression equations for continuous reference values for manual measurements are available online in Tables S1 and S2, respectively.

3.4 Agreement between automatic and manual measurements

The automatic measurements of MAPSE were lower than the manual measurements (P < .001), with mean difference ± SD = −1.4 ± 2.0 mm. There was no significant mean estimation bias between automatic and manual measurements of S’ (P = .13), with mean difference ± SD 0.0 ± 0.5 cm/s. The automatic measurements of e’ and a’ were slightly higher than the manual measurements (both P < .001), with mean difference ± SD = 0.4 ± 0.7 cm/s and 0.6 ± 0.8 cm/s, respectively. Limits of agreement are shown in the Bland–Altman plots in Figure 4. The CoV was 11.7% for MAPSE, 5.5% for S’, 6.3% for e’ and 9.9% for a’. As indicated in Figure 4, the measurement differences were weakly correlated to the magnitude of measurement values (r = −0.22 for MAPSE, r = 0.22 for S’, r = 0.18 for e’, and r = 0.08 for a’, all P < .001).

4 DISCUSSION

Normal reference values for automatically and manually measured mitral annular motion indices from a large, healthy population are presented. The automatic measurements acquired by a previously described method showed high feasibility and good agreement with manual measurements. The large sample size allows for generalization to adults of both genders within a wide range of age. Implementing the automatic measurements and comparison with normal ranges in ultrasound scanners can allow for quick and precise interpretation of LV function.

A key question is whether specific reference values for the automatic measurements are needed, or if reference values based on manual measurements can be used to interpret the automatic measurements. The automatic cTDI measurements of MAPSE were on average 1.4 mm lower than the manual M-mode measurements. This is in line with findings by others showing higher MAPSE by M-mode than by the cTDI method.19–21 This can primarily be explained by the use of autocorrelation in cTDI, where image clutter reduces the estimates. Also, there is opposite angle dependency in M-mode and cTDI. M-mode measurements increase while cTDI measurements decrease by the cosine of the angle between the ultrasound beam and the direction of motion. An angle error of 15 degrees leads to approximately 3.5% over- and underestimation by M-mode and cTDI, respectively, compared with true values parallel to the LV long axis. Furthermore, MAPSE by one-dimensional M-mode is prone to in- and out-of-plane movement of the myocardial wall which may lead to overestimation.22,23 As the cTDI method measures the Doppler shift in a broader area, it is less prone to out-of-plane errors. Thus, MAPSE measurements by cTDI and M-mode are not interchangeable.

For S’, e’, and a’, both the automatic and the manual measurements were cTDI-derived. Indices derived by pulsed wave tissue Doppler imaging (pwTDI) and cTDI differ, with higher absolute values by pwTDI.20,21 In the European initiative Normal Reference Ranges for Echocardiography Study, only pwTDI indices of mitral annular velocities were presented.24 Even though pwTDI spectra can be quickly interpreted, the possibility to place multiple regions of interest simultaneously is an advantage of cTDI. Furthermore, cTDI indices are less influenced by gain settings25 and form an ideal platform for automatic evaluation of both systolic and diastolic LV function. For evaluation of diastolic function, pwTDI is often preferred,
but as cTDI is sensitive to subclinical changes in LV function\textsuperscript{10,25,26} and carries prognostic information,\textsuperscript{27} it can be argued that it is underused in clinical practice.

The automatic measurements of $S'$ were in excellent agreement with the manual measurements. The diastolic velocity measurements showed a slightly lower, but still good, agreement. The agreement was in line with what has been shown for inter-observer agreement between experts.\textsuperscript{20} Despite statistically significant differences in means of automatic and manual measurements of MAPSE, $e'$, and $a'$, the differences and CoVs were in the middle of what has been reported previously for repeated manual measurements by M-mode, cTDI, and pwTDI,\textsuperscript{20,21,22} and such small variations have justified to use these modalities in clinical practice. To put the discrepancies in perspective, the CoVs of all indices in

| Table 2: Categorical reference values for automatic measurements of mitral annular motion indices |
|---------------------------------------------|
| | n | Mean | SD | Lower limit, mean - 1.96 SD | Upper limit, mean + 1.96 SD |
|---------------------------------------------|
| MAPSE (mm) | | | | | |
| Women | | | | | |
| <40 y | 189 | 15.2 | 1.8 | 11.6 | 18.8 |
| 40–59 y | 309 | 14.3 | 2.0 | 10.4 | 18.2 |
| ≥60 y | 110 | 12.3 | 2.0 | 8.3 | 16.3 |
| Men | | | | | |
| <40 y | 116 | 15.1 | 1.9 | 11.4 | 18.8 |
| 40–59 y | 299 | 14.0 | 2.2 | 9.7 | 18.2 |
| ≥60 y | 134 | 13.2 | 2.1 | 9.0 | 17.4 |
| $S'$ (cm/s) | | | | | |
| Women | | | | | |
| <40 y | 189 | 7.1 | 1.0 | 5.1 | 9.0 |
| 40–59 y | 309 | 6.6 | 1.1 | 4.5 | 8.6 |
| ≥60 y | 110 | 5.8 | 1.1 | 3.6 | 8.0 |
| Men | | | | | |
| <40 y | 116 | 7.5 | 1.2 | 5.2 | 9.8 |
| 40–59 y | 299 | 6.9 | 1.4 | 4.2 | 9.6 |
| ≥60 y | 134 | 6.5 | 1.3 | 4.0 | 9.0 |
| $e'$ (cm/s) | | | | | |
| Women | | | | | |
| <40 y | 189 | 11.3 | 1.8 | 7.9 | 14.8 |
| 40–59 y | 309 | 8.9 | 2.0 | 5.1 | 12.8 |
| ≥60 y | 110 | 6.3 | 1.7 | 3.0 | 9.6 |
| Men | | | | | |
| <40 y | 116 | 10.9 | 1.9 | 7.2 | 14.7 |
| 40–59 y | 299 | 8.4 | 2.0 | 4.6 | 12.3 |
| ≥60 y | 134 | 6.3 | 1.7 | 3.0 | 9.6 |
| $a'$ (cm/s) | | | | | |
| Women | | | | | |
| <40 y | 189 | 6.8 | 1.5 | 3.8 | 9.8 |
| 40–59 y | 309 | 7.9 | 1.4 | 5.2 | 10.6 |
| ≥60 y | 110 | 8.1 | 1.4 | 5.3 | 10.8 |
| Men | | | | | |
| <40 y | 116 | 7.0 | 1.7 | 3.7 | 10.2 |
| 40–59 y | 299 | 8.1 | 1.4 | 5.3 | 10.8 |
| ≥60 y | 134 | 8.7 | 1.5 | 5.8 | 11.7 |

Abbreviations: $a'$ = peak late diastolic mitral annular velocity; $e'$ = peak early diastolic mitral annular velocity; MAPSE = mitral annular plane systolic excursion; $S'$ = peak systolic mitral annular velocity; SD = standard deviation. Other abbreviations as in Table 1.
The automatic and manual measurements of $S'$ and $e'$ seem to be interchangeable for clinical use. MAPSE and $S'$ were closely correlated, and $S'$ had the highest agreement with the reference in this study. However, the present study does not support using $S'$ over MAPSE.

The relationship between the mitral annular motion indices, gender, age, and body surface area was as expected based on previous reports.\textsuperscript{10-14,24} Even though we found no overall association between gender and MAPSE, there was a small interaction effect between age and gender for MAPSE with more age dependency in women. We chose to present reference values with age categorized in approximately 20-year intervals, in addition to reference values utilizing age as a continuous variable. Among the four mitral annular indices in this study, $e'$ is probably the most utilized in clinical practice, as it is an important parameter for assessment of diastolic function. Current guidelines do not clearly recommend age-specific cut-off values,\textsuperscript{29} but due to its strong negative correlation with age, interpreting $e'$ with high emphasis on age might be beneficial. For example, the categorical lower limit for normalcy for women aged 59 years was 5.1 cm/s, while the continuous lower limit was 4.4 cm/s, a relative difference of 13.7%. The presented regression equations, either for the automatic or manual measurements, can be implemented on any ultrasound scanner. This may lead to faster...
interpretation and higher diagnostic accuracy. However, there is considerable overlap in mitral annular motion between healthy and diseased populations, and the limits of any prediction interval are not clear cutoffs.

The measurements in this study were based on the average of septal and lateral measurements, leaving out measurements from the base of the four other LV walls. As shown previously, the mean values of normal left ventricles are not influenced significantly by this simplified approach. However, measuring from four or six walls reduces the variance.10,11

The regions of interest for tracking of the mitral annulus must be correctly positioned for valid automatic measurements. Currently, the position of the tracking points must be checked in order to approve or discard measurements. Further development should evaluate the use of artificial intelligence for automatic evaluation of the tracking quality.

In post-hoc correlation analyses, the difference between automatic and manual measurements was compared against the participants’ ejection fraction (EF) and LV mass index. There was no association of measurement differences with EF, but a very weak association with LV mass index with $r = -0.09$ to $-0.10$, all $P \leq .01$ (Figure

### TABLE 3 Continuous reference values for automatic measurements of mitral annular motion indices

|       | a              | b              | n  | $t_{n-2,0.95}$ | s           | $\bar{x}$ | $s_x$   |
|-------|----------------|----------------|----|----------------|-------------|-----------|---------|
| MAPSE |                |                |    |                |             |           |         |
| Women | 17.982911      | -0.078405      | 608| 1.96388632     | 1.907227    | 48.054638 | 13.584971|
| Men   | 16.419584      | -0.047744      | 549| 1.96431031     | 2.087472    | 50.351913 | 13.613755|
| $S'$  |                |                |    |                |             |           |         |
| Women | 8.277763       | -0.035549      | 608| 1.96388632     | 1.038349    | 48.054638 | 13.584971|
| Men   | 8.212679       | -0.025377      | 549| 1.96431031     | 1.287098    | 50.351913 | 13.613755|
| $e'$  |                |                |    |                |             |           |         |
| Women | 16.056482      | -0.142402      | 608| 1.96388632     | 1.643957    | 48.054638 | 13.584971|
| Men   | 14.808078      | -0.126493      | 549| 1.96431031     | 1.743611    | 50.351913 | 13.613755|
| $a'$  |                |                |    |                |             |           |         |
| Women | 5.712799       | 0.039223       | 608| 1.96388632     | 1.441878    | 48.054638 | 13.584971|
| Men   | 5.662208       | 0.046335       | 549| 1.96431031     | 1.476167    | 50.351913 | 13.613755|

Note: The model is based on women aged 19–89 y, and men aged 19–83 y. Values for MAPSE are given in mm, values for $S'$, $e'$, and $a'$ are given in cm/s. For a person with age $x$, the mean expected value $\bar{y}$ for each mitral annular motion index can be expressed as $\bar{y} = a + bx$, where $a$ is a constant and $b$ is the regression coefficient for $x$. 95% of individuals aged $x$ years can be expected to have values of mitral annular motion indices of $\bar{y} \pm t_{n-2,0.95} \sqrt{\frac{1}{n} + \frac{(x-\bar{x})^2}{n(n-1)}} s$, where $s$ = standard deviation of residuals, $n$ = number of cases, $\bar{x}$ = mean age, $s_x$ = standard deviation of age, and $t_{n-2,0.95}$ critical value of a $t$ distribution with $n-2$ degrees of freedom (two-tailed at 95% confidence level). Other abbreviations as in Table 2.

FIGURE 4 Agreement between automatic and manual measurements of mitral annular motion indices. Each dot represents one of the 1157 cases. The blue lines indicate the mean differences, and the red dashed lines indicate the 95% limits of agreement. Differences are computed as automatic minus manual measurements. Abbreviations as in Figure 1
S1). This indicates that the automatic and manual measurements demonstrated similar agreement across grades of normal systolic LV function and morphology.

4.1 Study limitations

Most of the study participants were Caucasians of Northern European descent. Ethnicity may affect mitral annular motion indices. It is shown that a Chinese population had slightly different values compared with the Norwegian HUNT3 population. Like in all population studies, selection bias could have occurred. All the examinations were conducted by one experienced echocardiographer using equipment by a single vendor, and two experienced observers analyzed the echocardiograms. This assured high quality of the recordings and analyses, but the agreement may have been better than if more observers with different experience and more vendors were included. The method for automatic measurements has not been released as a commercial software, and implementing the method on ultrasound scanners would require research and development.

5 CONCLUSIONS

Reference values for automatic and manual measurements of mitral annular motion indices from a large, healthy population are presented. The automatic measurements showed good agreement with reference measurements by experienced echocardiographers. Implementing automatic measurements of mitral annular motion and comparison with normal ranges in ultrasound scanners can allow for quick and accurate interpretation of LV function.

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REFERENCES

1. Storve S, Grue JF, Samstad S, et al. Realtime automatic assessment of cardiac function in echocardiography. IEEE Trans Ultrasound Ferroelectr Freq Control. 2016;63:358–368.
2. Yamamoto T, Oki T, Yamada H, et al. Prognostic value of the atrial systolic mitral annular motion velocity in patients with left ventricular systolic dysfunction. J Am Soc Echocardiogr. 2003;16:333–339.
3. Willenheimer R, Cline C, Erhardt L, et al. Left ventricular atrioventricular plane displacement: an echocardiographic technique for rapid assessment of prognosis in heart failure. Heart. 1997;78:230–236.
4. Wang M, Yip G, Yu CM, et al. Independent and incremental prognostic value of early mitral annulus velocity in patients with impaired left ventricular systolic function. J Am Coll Cardiol. 2005;45:272–277.
5. Nikitin NP, Loh PH, De Silva R, et al. Prognostic value of systolic mitral annular velocity measured with Doppler tissue imaging in patients with chronic heart failure caused by left ventricular systolic dysfunction. Heart. 2006;92:775–779.
6. Grue JF, Storve S, Dalen H, et al. Automatic measurements of mitral annular plane systolic excursion and velocities to detect left ventricular dysfunction. Ultrasound Med Biol. 2018;44:168–176.
7. Anwar S, Negishi K, Borowszki A, et al. Comparison of two-dimensional strain analysis using vendor-independent and vendor-specific software in adult and pediatric patients. JRSM Cardiovasc Dis. 2017;6:2048004017712862.
8. Kjaergaard J, Korinek J, Belohlavek M, et al. Accuracy, reproducibility, and comparability of Doppler tissue imaging by two high-end ultrasound systems. J Am Soc Echocardiogr. 2006;19:322–328.
9. Mårtensson M, Bjillmark A, Brodin LA. Evaluation of tissue Doppler-based velocity and deformation imaging: a phantom study of ultrasound systems. Eur J Echocardiogr. 2011;12:467–476.
10. Dalen H, Thorstensen A, Vatten LJ, et al. Reference values and distribution of conventional echocardiographic Doppler measures and longitudinal tissue Doppler velocities in a population free from cardiovascular disease. Circ Cardiovasc Imaging. 2010;3:614–622.
11. Støylen A, Malmen HE, Dalen H. Relation between mitral annular plane systolic excursion and global longitudinal strain in normal subjects: the HUNT study. Echocardiography. 2018;35:603–610.
12. Nikitin NP, Witte K, Thackray S, et al. Longitudinal ventricular function: normal values of atrioventricular annular and myocardial velocities measured with quantitative two-dimensional color Doppler tissue imaging. J Am Soc Echocardiogr. 2003;16:906–921.
13. Yao GH, Zhang M, Yin LX, et al. Doppler echocardiographic measurements in normal chinese adults (EMINCA): a prospective, nationwide, and multicentre study. Eur Heart J Cardiovasc Imaging. 2016;17:512–522.
14. Peverill RE, Chou B, Donelan L. Left ventricular long axis tissue Doppler systolic velocity is independently related to heart rate and body size. PLoS ONE. 2017;12:1–19.
15. Kroekstad S, Langhammer A, Hveem K, et al. Cohort profile: the HUNT study, Norway. Int J Epidemiol. 2013;42:968–977.
16. Naghue SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr. 2009;10:165–193.
17. Gottidiener JS, Bednarz J, Devereux R, et al. American Society of Echocardiography recommendations for use of echocardiography in clinical trials: a report from the American Society of
Echocardiography’s guidelines and standards committee and the task force on echocardiography in clinical trials. J Am Soc Echocardiogr. 2004;17:1086–1119.

18. Dean A, Voss D. Design and Analysis of Experiments. New York, NY: Springer-Verlag; 1999:140.

19. Ballo P, Bocelli A, Motto A, et al. Concordance between M-mode, pulsed Tissue Doppler, and colour Tissue Doppler in the assessment of mitral annulus systolic excursion in normal subjects. J Eur J Echocardiogr. 2008;9:748–753.

20. De Knegt MC, Biering-Sørensen T, Sogaard P, et al. Concordance and reproducibility between M-mode, tissue Doppler imaging, and two-dimensional strain imaging in the assessment of mitral annular displacement and velocity in patients with various heart conditions. Eur J Echocardiogr. 2014;15:62–69.

21. Thorstensen A, Dalen H, Amundsen BH, et al. Reproducibility in echocardiographic assessment of the left ventricular global and regional function, the HUNT study. Eur J Echocardiogr. 2010;11:149–156.

22. Manouras A, Shala A, Nyktari E, et al. Are measurements of systolic myocardial velocities and displacement with colour and spectral Tissue Doppler compatible? Cardiovasc Ultrasound. 2009;7:29.

23. Olsen NT, Jons C, Fritz-Hansen T, et al. Pulsed-wave tissue doppler and color tissue doppler echocardiography: calibration with M-Mode, agreement, and reproducibility in a clinical setting. Echocardiography. 2009;26:638–644.

24. Caballero L, Kou S, Dulgheru R, et al. Echocardiographic reference ranges for normal cardiac Doppler data: results from the NORRE Study. Eur J Cardiovasc Imaging. 2015;16:1031–1041.

25. Mogelvang R, Sogaard P, Pedersen SA, et al. Tissue Doppler echocardiography in persons with hypertension, diabetes, or ischaemic heart disease: the Copenhagen City Heart Study. Eur Heart J. 2008;30:731–739.

26. Dokainish H, Sengupta R, Pillai M, et al. Assessment of left ventricular systolic function using echocardiography in patients with preserved ejection fraction and elevated diastolic pressures. Am J Cardiol. 2008;101:1766–1771.

27. Mogelvang R, Biering-Sørensen T, Jensen JS. Tissue Doppler echocardiography predicts acute myocardial infarction, heart failure, and cardiovascular death in the general population. Eur Heart J Cardiovasc Imaging. 2015;16:1331–1337.

28. Muraru D, Badano LP, Piccoli G, et al. Validation of a novel automated border-detection algorithm for rapid and accurate quantitation of left ventricular volumes based on three-dimensional echocardiography. Eur Heart J Cardiovasc Imaging. 2010;11:359–368.

29. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17:1321–1360.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The correlation between measurement differences (computed as automatic – reference) and left ventricular (LV) mass index.

\( \dot{a} = \text{peak late diastolic mitral annular velocity} \)

\( \dot{e} = \text{peak early diastolic mitral annular velocity} \)

\( \text{MAPSE} = \text{mitral annular plane systolic excursion} \)

\( S = \text{peak systolic mitral annular velocity} \)

Table S1. Categorical reference values for manual measurements of mitral annular motion indices

Table S2. Continuous reference values for manual measurements of mitral annular motion indices

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