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**Mitral Annular Plane Systolic Excursion and Global
 longitudinal strain in normal subjects, the HUNT study.
 Relations to age, body size and gender.**

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Complete List of Authors:	Støylen, Asbjørn; Norwegian University of Science and Technology, Circulation and Medical Imaging; Mølmen, Harald; Asgardstrand General Practice, Horten, Norway Dalen, Håvard; Levanger Hospital, Department of Medicine
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Relation between Mitral Annular Plane Systolic Excursion and Global longitudinal strain in normal subjects, the HUNT study.

Asbjørn Støylen, MD, Dr, Med^{a,b}, Harald E Mølmen, MD, PhD^{c,d} Håvard Dalen, MD, PhD^{a,b,e}.

a: Department of Medical Imaging and Circulation, Faculty of medicine, Norwegian University of Science and Technology, Trondheim, Norway. b: Department of Cardiology, St. Olav's University Hospital, Trondheim, Norway. c: Morbid Obesity Centre, Division of Medicine, Department of Endocrinology, Vestfold Hospital Trust, Tønsberg, Norway. d: Asgardstrand General Practice, Horten, Norway. e Department of Medicine, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway.

Corresponding author: Asbjørn Støylen, Professor,
Department of Circulation and Imaging,

Postal address:

NTNU, Det medisinske fakultet

Institutt for sirkulasjon og bildediagnostikk

Postboks 8905

7491 Trondheim, Norway

Telephone +47 48108880, Fax +47 72828372

E:mail: asbjorn.stoylen@ntnu.no

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Abstract

Background

Left ventricular (LV) systolic long axis shortening can be measured as Mitral Annular Plane Systolic excursion (MAPSE). Global longitudinal strain (GLS) is relative LV shortening, equivalent to normalizing MAPSE for LV length (MAPSEn). The objective of this study was to test whether normalizing LV shortening reduced biological variability of MAPSE due to normalizing for heart size and, possibly BSA. Secondly to provide normal reference values for MAPSE.

Methods and results

1266 subjects from the Nord-Trøndelag Health Study (HUNT), without evidence of heart disease were examined. MAPSE and wall lengths were measured in all three standard apical views, while GLS has been published previously. Mean MAPSE was 1.58 (0.25) cm, MAPSEn 16.3 (2.4)% and GLS 16.7 (2.4)%. All measures declined with age, correlation between -0.50 and -0.41. MAPSE was gender independent, and less BSA dependent than MAPSEn and GLS, while relative standard deviations (SD) were similar for all three measures.

Conclusions

MAPSE, MAPSEn and GLS have similar biological variability, which is mainly due to age variation, indicating they are equivalent in normal, and normalizing for bBSA do not reduce the variability. Normalizing MAPSE for LV length (MAPSEn and GLS) normalizes for one dimension only, inducing a systematic error, and increasing BSA and inducing gender dependence. Normal age related, gender independent values for MAPSE are provided.

Key words:

Left ventricular shortening; Mitral annular plane systolic excursion; Global longitudinal strain; Normalization.

Abbreviations list

EF: Ejection fraction

GLS: Global longitudinal strain

HUNT: Nord-Trøndelag Health Study

LV: Left ventricle

LVED: Left ventricular external diameter in diastole

LVL: Left ventricular length (mean wall length) in diastole

MAPSE: Mitral annular plane systolic excursion

MAPSEn: MAPSE divided by mean LV wall length

SD: Standard deviation

TAPSE: Tricuspid annular plane systolic excursion

Introduction

Systolic left ventricular (LV) shortening can be assessed by long-axis M-mode (Figure 1) as Mitral Annular Plane Systolic Excursion (MAPSE), which is proportional to ejection fraction (EF) in dilated heart failure (1, 2, 3, 4), but may be reduced despite normal EF, as in LV hypertrophy (5, 6), and especially in heart failure with preserved EF (7), which may constitute up to 50% of heart failure patients (8). Thus, MAPSE is a prognostic predictor in unspecified heart failure (9), while EF is not (10).

Global longitudinal strain (GLS) is another measure of long axis LV function, which is more sensitive than EF (11, 12), and is reduced in heart failure both with preserved and reduced EF (13, 14). GLS is customarily measured by speckle tracking, tissue Doppler, or by the segmental combined method (15). Regardless of method, LV systolic longitudinal strain is relative longitudinal change in length during systole: End-systolic length (Ls) minus end-diastolic length (Ld), normalized for end-diastolic length $[Ls-Ld]/Ld$ (16) both for segmental and wall measures. As the LV shortens during systole, systolic longitudinal strain is negative. Thus, GLS is equivalent to LV shortening (MAPSE) normalized for end-diastolic length (MAPSEn) as shown in Figure 1B, and both are measures of longitudinal strain. GLS and MAPSEn are presumably normalized for heart size (and thus body size) and would hypothetically have less biological variability than MAPSE, i.e. a narrower normal range. This might improve diagnostic discriminatory capability. However, to our knowledge, GLS has not proven diagnostically or prognostically superior to MAPSE in adults.

MAPSE differs between LV walls in healthy individuals (17), so for a global measure, measurements from different walls must be averaged (2, 3, 4, 7, 9, 18). Strain has relatively less intra individual variability between walls than MAPSE (15, 18), suggesting that variation in MAPSE between walls is related to variations in wall length.

The aims of this study were; 1) to test the hypothesis that MAPSEn and GLS have less biological variation in adults, and 2) to provide gender and age specific normal values for MAPSE from a large population of healthy subjects (the HUNT Study).

Methods

Study subjects

The study population has been comprehensively described previously (15, 19, 20). Subjects were recruited from the HUNT3 Study of 50,839 participants, by excluding patients with a history of heart disease, hypertension or diabetes. From the remaining population, a randomized sample was drawn and invited to the echocardiographic sub study. After exclusion of 30 patients due to significant pathological findings by echocardiography, the total study group consisted of 1266 subjects. All subjects in the HUNT Study gave written consent to participating in both main and sub studies, and the study with all sub studies were approved by the ethical committee. The present analyses are in the same acquisitions as in the previous papers, but the data are not reported previously. Population characteristics are given in Table 1.

Echocardiography

One experienced echocardiographer (HD) conducted all the examinations. Subjects were examined in left lateral supine position with a Vivid 7 scanner (version BT06, GE Vingmed Ultrasound, Horten, Norway). Transducers were phased-array matrix transducers (M3S and M4S). The examination included parasternal M-mode and apical four- and two chamber and apical long-axis views. Mean B-mode frame rate was 44 FPS. Long-axis M-mode through the mitral ring was reconstructed from apical B-mode recordings in the septal and lateral points in 4-chamber plane, inferior and anterior points in 2-chamber plane and anteroseptal and inferolateral points in the apical long-axis plane. Annular motion was measured in all six points as shown in Figure 1A. We calculated global MAPSE from two, four and six walls (two walls from four-chamber view, four walls from two- and four chamber views, six wall from the three standard views, respectively).

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3 Wall lengths were measured as a straight line from apical epicardium to the mitral ring points as
4 shown in fig 1B) in all six walls (three standard apical planes) and averaged to global LV wall length as a
5 measure of LV length (LVL). LV external diameter (LVED) was measured from M-mode as the sum of
6 LV internal diastolic diameter and the inferolateral and septal diastolic wall thickness. Data on the size
7 and geometry of the LV in this study have been published recently (20). MAPSEn was calculated as
8 MAPSE divided by wall length for each wall, and then averaged for global MAPSEn, from four and six
9 walls. GLS based on segmental measurements by combined tissue Doppler and speckle tracking (Figure
10 1B), have been published previously (15). Systolic GLS is per definition negative (shortening). For
11 comparison with MAPSE, in the present paper absolute values are given, and “higher strain” refers to
12 higher absolute values.
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26 *Calculation and statistics*

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28 Calculations and statistics were done in SPSS (IBM, corp). Echocardiographic indices are presented as
29 means and standard deviations (SD). Strain is given in numeric values. Differences between genders were
30 tested by independent samples student's *t*-test, differences between age groups by one-way ANOVA, and
31 differences between different means of MAPSE (two-, four and six walls) by within-subjects (repeated
32 measures) ANOVA, all with Bonferroni post-hoc comparisons. To compare the variability of indices
33 across different units, the relative SD (SD/mean) were used. To assess the effect and interaction of BSA,
34 age and gender, linear regression was used. Correlations were assessed by Pearson's correlation
35 coefficient.
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46 Repeatability of the different measures in this material has been extensively studied by inter
47 observer repeated measurements (test-retest) in previous studies. Shortly, mean error was 3% and
48 coefficient of repetition (CoR) was 0.7 cm for mean wall length (20) and 4% and 1.6 mm, respectively for
49 MAPSE (18). For GLS mean error was 6% relative and CoR was 2% points (17). In the present study,
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3 mean error was 3% and CoR was 1.6 mm for global MAPSE, with highest variability in the anteroseptal
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5 wall.

6 7 8 9 **Results**

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11 MAPSE, was shown to be normally distributed, with skewness 0.003 (SE 0.07), MAPSEn and GL very
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13 near normally distributed as shown in Figure 2, with a minimal, although significant skewness of -0.17
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15 and 0.19, respectively (both SE = 0.07). Age was likewise normally distributed, with no significant
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17 skewness.
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20 Age and gender related values for MAPSE and MAPSEn from four and six walls and GLS are
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22 given in Table 2. Both four and six walls are included in the discussion for comparison with GLS, which
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24 is measured in six walls. Feasibility of reconstructed M-mode was 95% in 4- and 2-chamber and 97% in
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26 apical long axis view. For comparison, feasibility of the segmental tissue Doppler/speckle tracking strain
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28 method was 60% of segments, as segments both above and below areas with clutter or drop outs had to be
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30 rejected (15), but over all feasibility was 95%. Relative standard deviations (SD/mean) are given in Table
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32 2. There were no differences between MAPSE and MAPSEn from four walls, although slightly higher
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34 variability for MAPSE from six walls. GLS had the highest relative SD.
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38 Mean MAPSE from two, four and six walls according to age are given in Table 3. When MAPSE
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40 was measured from two, four and six walls the differences were clinically negligible (0.2-0.7 mm,
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42 smallest difference between two and four walls), although statistically significant due to population size
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44 (all $p < 0.001$). There were only weak correlations between MAPSE and BSA as shown in table 4, and no
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46 relation to gender. MAPSEn and GLS were gender dependent, with approximately 1.5% (absolute) higher
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48 values in women (all $p < 0.001$), as shown in Table 2. Both, MAPSEn and GLS were negatively correlated
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50 with BSA, as illustrated in Figure 3. The difference between genders in BSA as shown in table 1, was
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52 highly significant ($p < 0.001$).and gender and BSA was not independent predictors of MAPSEn for four
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54 and six walls, but remained independent for GSL. Finally, MAPSE corrected for both LVED and LVL
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(MAPSE/LVL/LVED), showed only a trend for gender difference (1.10 cm vs 1.12 cm in men and women, respectively, $p = 0.06$), and a modest correlation with BSA ($r = 0.17$).

Age very weakly correlated with BSA ($r = -0.06$, $p = 0.04$). The result of multiple linear regressions with BSA and age are shown in Table 4. Age was the main predictor for MAPSE, MAPSEn and GLS, and was negatively correlated with all, as shown in fig 4. Differences between all age groups were highly significant ($p < 0.001$ overall and in all post hoc pairwise comparisons).

Discussion

The main finding is that MAPSE and global longitudinal strain measured both as MAPSEn and GLS have similar biological variability in adults, without improvement by normalizing for LV length, neither in MAPSEn nor GLS. The diagnostic discriminatory capability of a parameter is related to its variability and how the means differ between the normal and diseased populations. In this study, it seems that the variability is similar in both GLS and MAPSE. The main reason for this finding, is that age, not size, is the main factor in biological variation as shown in this study. Thus, adjusting for size dependent variability does not change overall variability. However, in this study, normalizing for LV length actually *increased* body size dependency as discussed later. As the measurement compound error increase by the sum of the errors of the single measures, for MAPSEn, the compound coefficient of variation (CoV) will be approximately 3%. GLS has previously shown to have a CoV of 3% (15). In the study population, the relative SD were 14-24%, indicating that most of the variation in GLS, MAPSE and MAPSEn is biological.

Size dependent variability of global MAPSE and GLS

The weak, but positive correlation between MAPSE and BSA (the larger hearts, the higher MAPSE) is not unexpected, but this correlation is too weak to induce gender dependence. The finding that normalization for LV length actually reverses, and also increases body size dependency as seen in Figure

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3, as well as induces gender dependency, might seem surprising. The Body weight/BMI/BSA and gender
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5 dependence of GLS is well established (15, 21, 22, 23). Gender or BSA dependency has never, to our
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7 knowledge been established for MAPSE. A possible explanation is that global LV shortening is related to
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9 three dimensions, while MAPSEn and GLS only corrects for one dimension – length, as shown in fig 5.
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11 We have previously shown that the ratio between LV length and LV diameter is BSA independent, so
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13 diameter and length are co variant, thus LV diameter influences longitudinal deformation as shown in
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15 figure 5. Normalizing only for length induces a systematic error, increasing the heart size (and hence,
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17 body size) dependency. This systematic error seems to be due to geometry, not to a specific method for
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19 global strain, as it is present for both GLS and MAPSEn. Gender dependency seems to be mostly due to
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21 BSA. Normalizing MAPSE for both wall length and external diameter, being more geometrically correct,
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23 reduced BSA dependency and eliminated gender differences. However, normalizing MAPSE for both
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25 wall length and external diameter seems unnecessary from a clinical point of view.
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31 *MAPSE and GLS global parameters of systolic LV function*

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33 MAPSE and GLS have similar variability, and thus may be equivalent for clinical use.
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36 But in addition to the systematic error induced by the normalization for LV length, there are
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38 differences between the methods. MAPSE is acquired by the generic method of M-mode, either by real-
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40 time acquisition or by reconstructed M-mode. (The difference in sampling rate between these two modes is
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42 of little consequence, as movement of the mitral ring is near zero at end-systole and end-diastole).
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44 Feasibility is high, even using reconstructed M-mode and reproducibility is good. Being gender
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46 independent, it might be advantageous as a measure of LV longitudinal function, although gender
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48 differences were on the order of 4% relative, compared with a ME of 6% relative. MAPSE is less BSA
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50 dependent, but by looking at the relative SD in each age group (Table 2) there is no clinically important
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52 difference between MAPSE and the normalized measures. Finally, MAPSE has the additional advantage
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54 that as Tricuspid Annular Plane Systolic Excursion (TAPSE) is recommended for assessment of right
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3 ventricular function (24), using MAPSE for the left ventricle gives comparable measures for both
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5 ventricles. Normal values for MAPSE are provided in table 3. The main convention in previous studies
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7 has been to use four-point average for global MAPSE (2, 3, 4, 5, 6, 7). The mean differences between
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9 two- four- and six-walls average are less than 1 mm, which is equal to the smallest measurement
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11 differences achievable by most commercial available software. Thus, the difference is clinically
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13 negligible, although statistically significant due to the large study population. However, test-retest
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15 reproducibility was improved by approximately 35% by using four walls instead of 2 (18). The present
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17 study shows that MAPSE from four walls had lower variability than MAPSE from six walls. This may be
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19 due to alignment problems in the apical long-axis views, similarly to what have been shown for
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21 measurements of wall length (20). Thus, four-wall average seems to be optimal for global MAPSE.

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24 All indices of LV long-axis function are lower in older age groups (Tables 2, 3 and Figure 3), as
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26 are systolic tissue velocities and diastolic functional measures (19). This raises the same question, as for
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28 diastolic function, and for relative wall thickness (20). Using age related normal values, will give a
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30 relatively constant abnormal percent, while constant normal values will result in higher prevalence of
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32 pathology with higher age. The answer to this is not a simple one. Using age adjusted normal limits ~~is~~
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34 ~~advocated also~~ for MAPSE, the lower limit of the reference range (mean-2SD) is 1.33 cm in the youngest
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36 age group (<40 years) and 0.96 cm in the oldest age group (≥ 60 years). A pragmatic view is that a lower
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38 limit of 1 cm excludes more serious pathology, as shown in previous studies (2, 3, 9), and illustrated in
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40 Figure 3, but at the cost of a reduced sensitivity in younger subjects. The clinical importance of this,
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42 however, is uncertain.

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46 Global strain methods today are mostly based on speckle tracking algorithms that are vendor
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48 dependent, with differences in GLS between vendors of up to 3.7 % points (similar to approximately 20%
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50 relative difference) (25). Even different software versions from the same vendor may provide different
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52 values (26). A joint industry and society initiative is under way to reduce the software dependency, but so
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54 far the main result is standards for definitions (27). However, much of the technological differences are
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3 still industrial secrets related to software algorithms, such as choice of kernel sizes, selection and
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5 weighting of acoustic markers, stability of speckles and drift compensation during heart cycle, as well as
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7 spline smoothing, which on the other hand ensures good reproducibility also for GLS.
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10 MAPSEn, on the other hand, is a generic, and non-vendor dependent method for global strain, as
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12 well as quick to acquire, easy and reproducible. It is not free from assumptions, but these are generic and
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14 evident. Thus, it is an alternative method for global longitudinal strain. However, the present study does
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16 not support using MAPSEn over MAPSE. The values for global longitudinal strain by both methods in
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18 this study, are lower than in many speckle tracking studies as shown in a recent meta analysis (23), where
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20 mean GLS was 19.7%. As most newer studies of GLS are performed by the use of speckle tracking (with
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22 different algorithms), there may be different issues as well, such as curvature dependency, sensitivity to
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24 foreshortening etc. Thus, normal values will differ by methods, as also discussed in the limitation section.
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26 This is reflected in the fact that the current guidelines (24) do not recommend normative values.
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29 M-mode measurements are angle dependent, but it is a misconception that speckle tracking
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31 derived GLS is angle independent. The angle dependency of speckle tracking, depends on the lateral vs.
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33 the axial resolution, and angle distortion may occur. GLS is also vulnerable to processing differences.
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36 In the present study, we compared average values from both four and six walls, to ensure that
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38 findings would not be due to difference in the number of walls between MAPSE and GLS. GLS is most
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40 often assessed in a 16-segment model, and thus, from six walls, and concerns have been raised about
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42 whether four walls will be representative for global systolic LV function in the presence of regional
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44 dysfunction. This concern rests partly on a common misconception that regional dysfunction affects
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46 chiefly the adjacent point of the mitral annulus, which is not the case (4).
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49 It must be emphasized that the present study addresses global LV function only. Strain and strain
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51 rate imaging remain valuable methods for quantifying segmental LV dysfunction and differences in
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53 timing, while regional MAPSE is not (4). Segmental function is important in e.g. coronary artery disease,
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55 conduction abnormalities and mechanical dispersion.
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Limitations

The HUNT Echocardiographic Study is among the largest studies of healthy individuals, selected from a general population study by independent criteria for normalcy. As seen from Table 1, the average BMI is at the upper normal limit, indicating that half the population is overweight. However, this is a common finding in many countries today, and compared to the general HUNT3 population values for BMI were slightly lower in the echocardiographic sub study (28). In addition, the indices of LV dimensions in this material is in line with other studies (20), indicating that the study population should be representative. Generalizability is limited by lack of ethnic and geographical diversity. However, for the discussion of GLS vs. MAPSE, this is less important, although the reference values may differ. Also, as this is a cross sectional study, the age differences are between cohorts, not related to true ageing.

Wall length measurements were done in straight lines from apex to the mitral ring, underestimating the true length of the curved wall, ~~but the mean overestimating the length of the LV as shown in Figure 1.~~ The advantage of this is reduced variability, compared to the more random assessment of the length of the curved wall or locating the correct midpoint of the annular plane. Also, this eliminates angle dependency when measuring MAPSEn. GLS, conforming more to the curved wall, has higher variability. The mean wall length is overestimating the length of the LV as shown in Figure 1. LV length can be calculated from mean LVL and wall thicknesses and diameters (20), giving a LV diastolic length of 77 mm, resulting in a mean MAPSEn of 20%. However, this makes the method more cumbersome, and do not change the main findings of the study.

The present study is limited to the variability of normal measurements, and the subsequent normal ranges, ~~and do not study the separation of means between normal and patient populations.~~ The diagnostic and prognostic capability should be studied head-to-head in comparative studies including patients with different pathology.

Conclusions

The hypothesis that normalizing MAPSE for LV length, or using GLS, reduces biological variability is not confirmed, as normal biological variability is the same for all measures. Thus, and it cannot be inferred that diagnostic discriminatory capability is higher for GLS than MAPSE. Head to head comparison studies in different patient cohorts, with respect to both diagnostic accuracy and prognostic

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References

1. Simonson JS, Schiller NB. Descent of the base of the left ventricle: an echocardiographic index of left ventricular function. *J Am Soc Echocardiogr* 1989;2:25-35
2. Höglund C, Alam M, Thorstrand C. Effects of acute myocardial infarction on the displacement of the atrioventricular plane: an echocardiographic study. *J Intern Med* 1989 Oct;226(4):251-6
3. Alam M, Höglund C, Thorstrand C, Philip A. Atrioventricular plane displacement in severe congestive heart failure following dilated cardiomyopathy or myocardial infarction. *J Intern Med* 1990 Dec;228(6):596-75
4. Stoylen A, Skjaerpe T. Systolic long axis function of the left ventricle. Global and regional information. *Scand Cardiovasc J.* 2003 Sep;37(5):253-8.
5. Wandt B, Bojö L, Tolagen K, Wranne B. Echocardiographic assessment of ejection fraction in left ventricular hypertrophy. *Heart.* 1999 Aug;82(2):192-8.
6. Emilsson K, Wandt B. The relation between mitral annulus motion and ejection fraction changes with age and heart size. *Clin Physiol.* 2000 Jan;20(1):38-43.

- 1
2
3 7. Vinereanu D, Nicolaidis E, Tweddel AC, Fraser AG. "Pure" diastolic dysfunction is associated
4 with long-axis systolic dysfunction. Implications for the diagnosis and classification of heart
5 failure. *Eur J Heart Fail*. 2005 Aug;7(5):820-8.
6
7
- 8
9 8. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function;
10 epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol*. 2004 Feb 4;43(3):317-
11 27.
12
13
- 14
15 9. Willenheimer R, Cline C, Erhardt L, Israelsson B. Left ventricular atrioventricular plane
16 displacement: an echocardiographic technique for rapid assessment of prognosis in heart failure.
17 *Heart* 1997;78:230-36.
18
19
- 20
21 10. Muntwyler J, Abetel G, Gruner C, Follath F. One-year mortality among unselected outpatients
22 with heart failure. *Eur Heart J*. 2002 Dec;23(23):1861-6.
23
24
- 25
26 11. Chan J, Hanekom L, Wong C, Leano R, Cho GY, Marwick TH. Differentiation of subendocardial
27 and transmural infarction using two-dimensional strain rate imaging to assess short-axis and long-
28 axis myocardial function. *J Am Coll Cardiol*. 2006 Nov 21;48(10):2026-33.
29
30
- 31
32 12. Gjesdal O, Helle-Valle T, Hopp E, Lunde K, Vartdal T, Aakhus S, Smith HJ, Ihlen H, Edvardsen
33 T. Noninvasive separation of large, medium, and small myocardial infarcts in survivors of
34 reperused ST-elevation myocardial infarction: a comprehensive tissue Doppler and speckle-
35 tracking echocardiography study. *Circ Cardiovasc Imaging*. 2008 Nov;1(3):189-96
36
37
- 38
39 13. Ersbøll M, Valeur N, Mogensen UM, Andersen MJ, Møller JE, Velazquez EJ, Hassager C,
40 Sogaard P, Køber L. Prediction of all-cause mortality and heart failure admissions from global left
41 ventricular longitudinal strain in patients with acute myocardial infarction and preserved left
42 ventricular ejection fraction. *J Am Coll Cardiol*. 2013 Jun 11;61(23):2365-73.
43
44
- 45
46 14. Stampehl MR, Mann DL, Nguyen JS, Cota F, Colmenares C, Dokainish H. Speckle strain
47 echocardiography predicts outcome in patients with heart failure with both depressed and
48 preserved left ventricular ejection fraction. *Echocardiography*. 2015 Jan;32(1):71-8.
49
50
- 51
52
53
54
55
56
57
58
59
60

- 1
2
3 15. Dalen H, Thorstensen A, Aase SA, Ingul CB, Torp H, Vatten LJ, Støylen A. Segmental and global
4 longitudinal strain and strain rate based on echocardiography of 1266 healthy individuals: the
5 HUNT study in Norway. *Eur J Echocardiogr.* 2010 Mar;11(2):176-83.
6
7
- 8
9 16. Mirsky I, Parmley WW. Assessment of Passive Elastic stiffness for isolated heart muscle and the
10 intact heart. *Circ Res* 1973;33: 233-243.
11
12
- 13 17. Mondillo S, Galderisi M, Ballo P, Marino PN; Study Group of Echocardiography of the Italian
14 Society of Cardiology. Left ventricular systolic longitudinal function: comparison among simple
15 M-mode, pulsed, and M-mode color tissue Doppler of mitral annulus in healthy individuals. *J Am*
16 *Soc Echocardiogr.* 2006 Sep;19(9):1085-91.
17
18
- 19 18. Thorstensen A, Dalen H, Amundsen BH, Aase SA, Stoylen A. Reproducibility in
20 echocardiographic assessment of the left ventricular global and regional function, the HUNT
21 study. *Eur J Echocardiogr.* 2010 Mar;11(2):149-56.
22
23
- 24 19. Dalen H, Thorstensen A, Vatten LJ, Aase SA, Stoylen A. Reference Values and Distribution of
25 Conventional Echocardiographic Doppler Measures and Longitudinal Tissue Doppler Velocities
26 in a Population Free from Cardiovascular Disease. 2010 Sep 1;3(5):614-22.
27
28
- 29 20. Stoylen A, Mølmen HE, Dalen H. Importance of length and external diameter on left ventricular
30 geometry. Normal values from the HUNT Study. *Open Heart* 2016;3:e000465.
31
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58
59
60
doi:10.1136/openhrt-2016-000465
21. Marwick TH, Leano RL, Brown J, Sun JP, Hoffmann R, Lysyansky P et al. Myocardial strain
measurement with 2-dimensional speckle-tracking echocardiography: definition of normal range.
JACC Cardiovasc Imaging. 2009; 2:80-84.
22. Sun JP, Lee AP, Wu C, Lam YY, Hung MJ, Chen L et al. Quantification of left ventricular
regional myocardial function using two-dimensional speckle tracking echocardiography in healthy
volunteers--a multi-center study. *Int J Cardiol.* 2013; 167:495-501.

- 1
2
3 23. Yingchoncharoen T, Agarwal S, Popović ZB, Marwick TH. Normal ranges of left ventricular
4 strain: a meta-analysis. *J Am Soc Echocardiogr*. 2013; **26**:185-191.
5
6
7 24. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster
8 E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L,
9 Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by
10 echocardiography in adults: an update from the American Society of Echocardiography and the
11 European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015 Jan;**28**(1):1-39.
12
13
14
15
16
17 25. Farsalinos KE, Daraban AM, Ünlü S, Thomas JD, Badano LP, Voigt J-U. Head-to-head
18 comparison of global longitudinal strain measurements among nine different vendors. *J Am Soc*
19 *Echocardiogr* 2015;**28**:1171-81.
20
21
22
23
24 26. Nagata Y, Takeuchi M, Mizukoshi K, Wu VC, Lin FC, Negishi K, Nakatani S, Otsuji Y.
25 Intervendor variability of two-dimensional strain using vendor-specific and vendor-independent
26 software. *J Am Soc Echocardiogr*. 2015 Jun;**28**(6):630-41.
27
28
29
30
31 27. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, Pedri S, Ito Y, Abe Y,
32 Metz S, Song JH, Hamilton J, Sengupta PP, Koliass TJ, d'Hooge J, Aurigemma GP, Thomas JD,
33 Badano LP. Definitions for a common standard for 2D speckle tracking echocardiography:
34 consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging.
35 *Eur Heart J Cardiovasc Imaging*. 2015 Jan;**16**(1):1-11.Mar;**16**(3):233-70.
36
37
38
39
40
41 28. Midthjell K, Lee CM, Langhammer A, Krokstad S, Holmen TL, Hveem K, Colagiuri S, Holmen
42 J. Trends in overweight and obesity over 22 years in a large adult population: the HUNT Study,
43 Norway. *Clin Obes*. 2013 Feb;**3**(1-2):12-20.
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Tables

Table 1. Basic measurements of the study population.

	Women	Men	Total
N	663	603	1266
Age (years)	47.8 (13.5)	50.5 (13.7)	49.1 (13.7)
Height (m)	1.65 (0.11)	1.79 (0.07)	1.72 (0.12)
Weight (Kg)	71.6 (14.0)	87.1 (30.7)	79.0 (24.7)
BMI (Kg/m²)	25.9 (4.2)	26.8 (3.5)	26.3 (3.9)
BSA (m²)	1.79 (0.16)	2.05 (0.16)	1.91 (0.20)
BP systolic/diastolic (mmHg)	127/71 (17/10)	133/77 (14/10)	130/74 (16/10)

Measurements are mean (SD). Abbreviations: BMI; body mass index, BSA; body surface area, BP; blood pressure, N; numbers.

Table 2. Normal values for MAPSE, normalized MAPSE and GLS according gender and age.

Age (years)	MAPSE (cm) (4 walls)	MAPSE (cm) (6 walls)	MAPSEn (%) (4 walls)	MAPSEn (%) (6 walls)	GLS (%) from (15)
Women					
<40	1.73 (0.20)	1.67 (0.33)	18.1 (2.0)	17.8 (2.4)	17.9 (2.1)
40-60	1.58 (0.23)	1.50 (0.34)	17.0 (2.2)	16.6 (2.2)	17.6 (2.1)
>60	1.33 (0.22)	1.27 (0.29)	14.8 (2.1)	14.3 (2.4)	15.9 (2.4)
All	1.58 (0.26)	1.52 (0.36)	17.0 (2.4)	16.6 (2.5)	17.4 (2.3)
Men					
<40	1.72 (0.22)	1.66 (0.34)	16.5 (2.0)	16.6 (2.0)	16.8 (2.0)
40-60	1.58 (0.22)	1.50 (0.33)	15.4 (1.9)	15.0 (2.0)	15.8 (2.0)
>60	1.45 (0.23)	1.37 (0.34)	14.9 (1.9)	14.3 (2.4)	15.4 (2.4)
All	1.58 (0.24)	1.50 (0.35)	15.5 (2.0)	15.1 (2.2)	15.9 (2.3)
Total	1.58 (0.25)	1.51 (0.35)	16.3 (2.4)	15.9 (2.5)	16.7 (2.4)
Relative SD	0.16	0.23	0.14	0.16	0.24

Abbreviations: MAPSE: Mitral Annular Plane Systolic Excursion. MAPSEn: Normalized MAPSE =

MAPSE/mean wall length. GLS: Global longitudinal strain. Standard deviations in parentheses. Relative

SD: Standard deviation/mean.

Table 3. Normal values for systolic motion per myocardial wall and averaged MAPSE according to age.

Age (years)	N	MAPSE (2 walls)	MAPSE (4 walls)	MAPSE (6 walls)
<40	330	1.69 (0.21)	1.73 (0.20)	1.67 (0.33)
40-60	656	1.55 (0.24)	1.58 (0.23)	1.51 (0.34)
>60	264	1.39 (0.25)	1.40 (0.22)	1.32 (0.32)
All	1250	1.56 (0.26)	1.58 (0.25)	1.51 (0.35)

All motion values in cm. Standard deviations in parentheses. All means (of two, four and six walls) were significantly different ($p < 0.001$) from each other. Differences between age groups were all significant $p < 0.001$ in post hoc. There were no gender differences. Abbreviations: As in table 2.

Table 4. Relations between MAPSE, MAPSEn and GLS to age, gender and BSA in multiple linear regressions.

Measure		R (univariate)	β	p
MAPSE (four walls)	Age	-0.50	-0.49	<0.001
	BSA	0.12	0.10	<0.001
MAPSE (six walls)	Age	-0.37	-0.37	<0.001
	BSA	0.08	0.07	<0.05
MAPSEn (four walls)	Age	-0.41	-0.43	<0.001
	BSA	-0.23	-0.25	<0.001
MAPSEn (six walls)	Age	-0.41	-0.42	<0.001
	BSA	-0.22	-0.24	<0.001
GLS	Age	-0.27	-0.28	<0.001
	BSA	-0.27	-0.28	<0.001

Abbreviations: as in Table 2.

Table 5. Intra-individual variability between walls

	Mean	Intra-individual variance	Relative intra-individual variance (%)
Wall length (4 walls)	9.5 cm	0.21 cm	2
MAPSE (4 walls)	1.58 cm	0.04 cm	2.5
Normalized MAPSE (4 walls)	16.3 (% points)	0.04	0.2
Wall length (6 walls)	9.5 cm	0.50 cm	5.2
MAPSE (6 walls)	1.51 cm	0.06 cm	3.9
Normalized MAPSE (6 walls)	15.9 (% points)	0.06	0.4
GLS	16.7 (% points)	0.12	0.7

Absolute and relative intra-individual variances and relative variances in four and six walls calculated for each subject. Differences between non-normalized MAPSE and all normalized measures $p < 0.001$.

Abbreviations: As in Table 2.

Figure legends

Figure 1. Mitral Annular Plane Systolic Excursion (MAPSE), normalization of left ventricular shortening and global longitudinal strain (GLS).

A: Annular motion can be easily and robustly measured in apical recordings as the vertical difference between end-diastole and end-systole along the M-mode line through the mitral annulus. For global measures of MAPSE, the average of two, four or six walls should be used. **B:** LV shortening is the difference between systolic and diastolic lengths; $[L_d - L_s]$, and can be approximated by mean MAPSE. Global strain is LV shortening normalized for end diastolic length $[L_d - L_s]/L_d$ (white lines). MAPSE divided by wall lengths (WL) is normalized wall shortening and will be approximately equal to wall strain (normalized MAPSE ($MAPSE_n = \text{mean MAPSE}/WL$)). Diastolic length of the straight line from apex to the mitral ring (green solid lines), underestimates the length of the curved wall (green broken lines), while overestimating the length of the ventricle (L_s). However, the WL will be approximately parallel with the M-mode line, thus eliminating angle discrepancy. The yellow dotted lines with quadratic kernels illustrate GLS measured by the segmental method, tracking kernel motion and calculating segmental strain by segmental shortening. This is closer to the true wall length.

Figure 2. Normal distributions of MAPSE, $MAPSE_n$ and GLS

The figure shows the distribution of MAPSE, $MAPSE_n$ and GLS, showing all to be fairly normally distributed. Normal distribution is added for comparison. Abbreviations as in Figure 1.

Figure 3. Relations of MAPSE, $MAPSE_n$ and GLS to BSA. The figure shows a weak tendency of MAPSE to increase with increasing BSA, although the tendency is slight, and not enough to induce gender difference. The large variability is biological, as MAPSE has the lowest measurement variability, and is mostly due to age dependency.

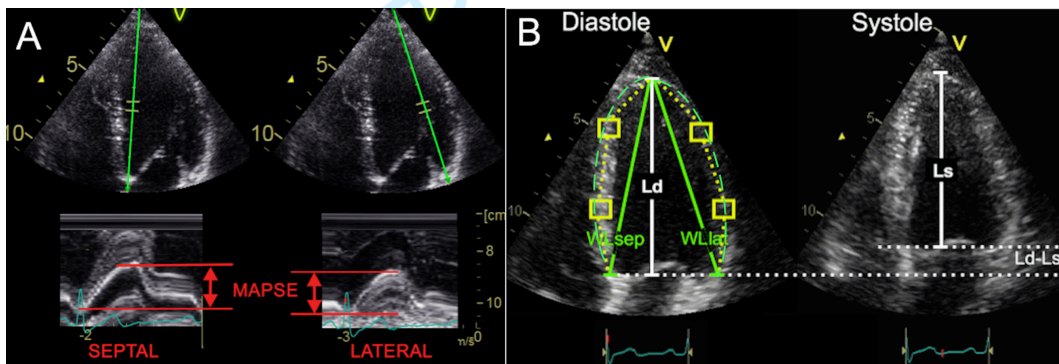
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3 **Figure 4. Age distributions of MAPSE, MAPSEn and GLS**

4 MAPSE and MAPSEn are assessed from four walls, as this is most feasible as discussed in the text.

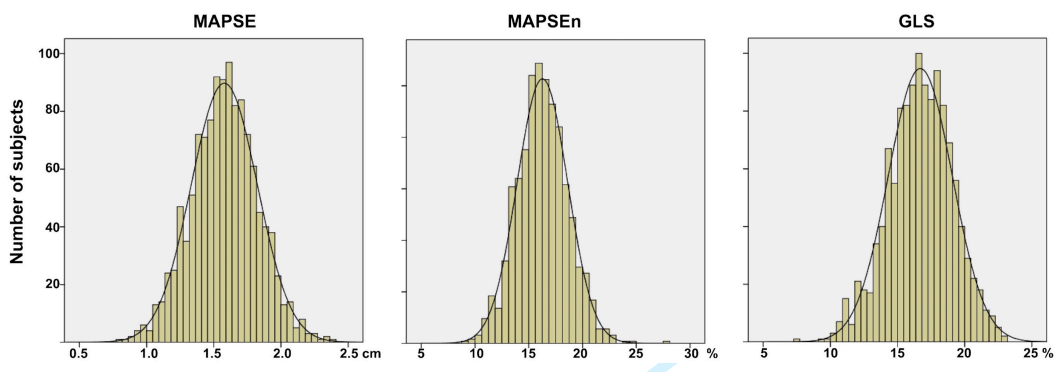
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7 Age related normal limits seems to be warranted. The empiric cut off for MAPSE of 1 cm is indicated by
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9 the red dotted line on the left diagram. As the figure shows, it will exclude serious pathology in most age
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11 groups, with a slight reduction in specificity > 60 years, and a more profoundly reduced sensitivity below
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13 40 years. Lower correlation with age for GLS seems to be mostly due to wider variance.
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18 **Figure 5. Simplified diagram of the relation between MAPSE, stroke volume and LV size.**

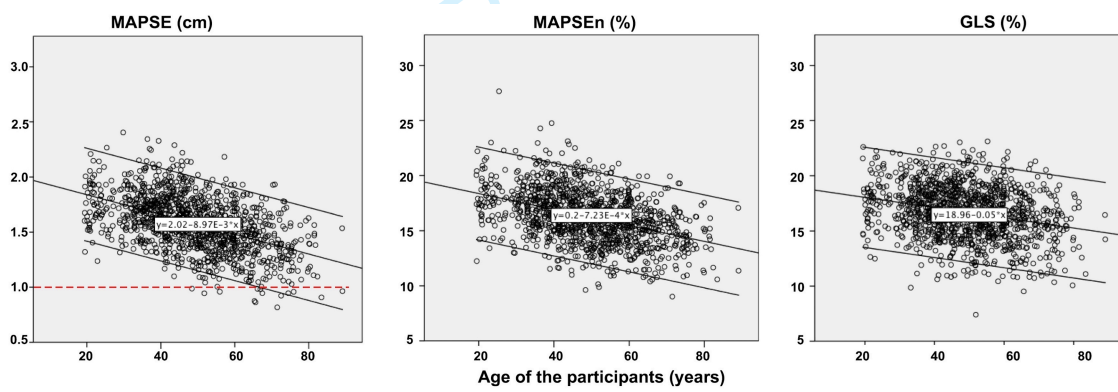
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20 Comparing two ventricles with equal MAPSE, but different sizes, 1 (left) and 2 (right). Total left
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22 ventricular volume change is a function of the MAPSE and the cross sectional surface. If the myocardium
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24 is incompressible, the wall volume must remain constant, while the total volume reduction must equal
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26 cavity volume reduction, i.e. stroke volume (red shading). The stroke volume is greater in the largest
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28 ventricle: $SV_2 > SV_1$, due to the larger cross sectional surface. But as $L_2 > L_1$, normalizing MAPSE for
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30 L_2 will result in a lower strain value than L_1 : $MAPSE/L_1 > MAPSE/L_2$, the inverse relation of the stroke
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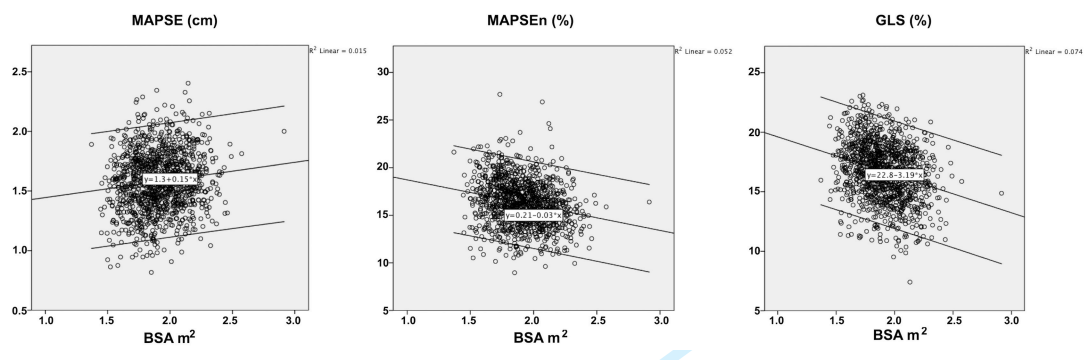
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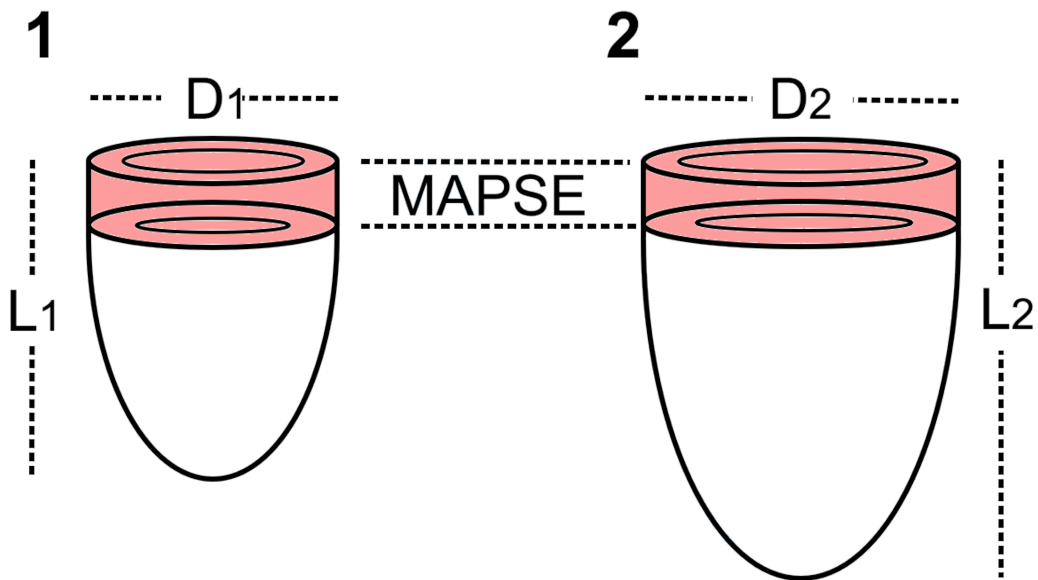


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