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Normal reference values of left ventricular strain using three-dimensional speckle tracking echocardiography: results from a multicentre study

Sebastiaan A. Kleijn[1]*, Natesa G. Pandian[2], James D. Thomas[3], Leopoldo Perez de Isla[4], Otto Kamp[1], Michel Zuber[5], Petros Nihoyannopoulos[6], Tamas Forster[7], Hans-Joachim Nesser[8], Annette Geibel[9], Willem Gorissen[10], and Jose L. Zamorano[11]

[1]Department of Cardiology 5F 003, VU University Medical Center, 1117 De Boelelaan, 1081 HV Amsterdam, the Netherlands; [2]Tufts Medical Center, Boston, MA, USA; [3]Cleveland Clinic, Cleveland, OH, USA; [4]Hospital Carlos III, Madrid, Spain; [5]Luzerner Kantonsspital, Luzern, Switzerland; [6]Hammersmith Hospital, London, UK; [7]University of Szeged, Szeged, Hungary; [8]Elisabethinen Hospital, Linz, Austria; [9]University Hospital Freiburg, Freiburg, Germany; [10]Toshiba Medical Systems, Zoetermeer, the Netherlands; and [11]Hospital Ramón y Cajal University Alcala de Henares, Madrid, Spain

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Aims Three-dimensional (3D) speckle tracking echocardiography (3DSTE) has been shown to be an accurate and reliable clinical tool for the evaluation of global and regional left ventricular (LV) function through strain analysis, but the absence of normal values has precluded its widespread use in clinical practice. The aim of this prospective multicentre study was to establish normal reference values of LV strain parameters using 3DSTE in a large healthy population.

Methods and results A total of 303 healthy subjects (156 males [51%], between 18 and 82 years of age, ejection fraction [EF] 61 ± 3%), stratified to provide approximately equal proportions of healthy subjects of 18–30, 31–40, 41–50, 51–60, and >60 years of age, underwent 3DSTE. Data were analysed for LV volumes, EF, mass, and global and regional circumferential, longitudinal, radial, and area strain. Significant but small differences between men and women were found for longitudinal and area strains, as well as between different age groups for all LV strain parameters. However, large differences in normal values were observed between different segments, walls, and levels of the LV for radial and longitudinal strains, whereas circumferential and area strains demonstrated generally consistent normal ranges across the LV.

Conclusions Normal ranges of global and regional LV strain using 3DSTE have been established for clinical use. Differences in the magnitude of LV strain are present between men and women as well as different age groups. Moreover, there are differences between different segments, walls, and levels as part of the functional non-uniformity of the normal LV that necessitates the use of segment-specific normal ranges for radial and longitudinal strains. Circumferential and area strains demonstrate the most consistent normal ranges overall.

Keywords Three-dimensional imaging • Echocardiography • Speckle tracking • Left ventricular function

Introduction

Three-dimensional (3D) speckle tracking echocardiography (3DSTE) has previously been shown to be an accurate and reliable clinical tool for the evaluation of left ventricular (LV) volumes and ejection fraction (EF), as well as global and segmental myocardial function through strain analysis in different patient populations.[1–12] However, the lack of clearly defined normal ranges of strain parameters has currently precluded their widespread use in clinical practice. In addition to patient-specific factors such as age and gender that may influence strain parameters, previous studies have also demonstrated the presence of functional non-uniformity of the normal LV, which may necessitate the

* Corresponding author. Tel: +31 20 444 2244; Fax: +31 20 444 2446, Email: s.kleijn@vumc.nl

use of site-specific normal ranges.[5,13,14] Therefore, the aim of this prospective multicentre study was to establish reference values of global and segmental LV strain parameters using 3DSTE in a large healthy population.

Methods

Study population

From June 2011 to July 2013, a total of 303 healthy Caucasian subjects were enrolled in the study from 10 different sites located in eight different countries in Europe and the USA, namely Elisabethinen Hospital, Linz, Austria; University Hospital Freiburg, Freiburg, Germany; University of Szeged, Szeged, Hungary; VU University Medical Center, Amsterdam, the Netherlands; Hospital Carlos III and Hospital Clínico San Carlos, Madrid, Spain; Luzerner Kantonsspital, Luzern, Switzerland; Hammersmith Hospital, London, UK; Tufts Medical Center, Boston, USA; and Cleveland Clinic, Cleveland, USA. Recruitment was stratified to provide approximately equal proportions of healthy subjects of 18–30, 31–40, 41–50, 51–60, and >60 years of age. The sample size is based on the width of the 95% confidence interval for the mean (precision) of 1.11–3.88% for the different global strains and 2.77–8.30% for the segmental strains based on previous work.[5,7] Subjects had no history of cardiac symptoms, hypertension or diabetes, no use of medication and normal physical cardiac examination, electrocardiogram, and echocardiogram. All subjects gave informed consent to participate in the study and the ethics committee of each individual hospital approved the study.

Echocardiographic imaging

3DSTE imaging was performed from an apical position using a commercial scanner (Artida 4D, Toshiba Medical Systems) with a fully sampled matrix array transducer (PST-25SX). Wide-angled acquisitions were recorded, in which four to six wedge-shaped sub-volumes were acquired over consecutive cardiac cycles during a single breath-hold. While retaining the entire LV within the pyramidal volume, depth and sector width were decreased as much as possible to improve the temporal and spatial resolution of the images, resulting in a mean temporal resolution of 20 ± 2 volumes per second. 3DSTE images were then stored digitally and transferred to the echo core laboratory at the VU University Medical Center, Amsterdam, the Netherlands, for offline analysis. Datasets that excluded a portion of the LV, had indistinct endocardial borders, stitch artefacts, or poor temporal resolution were excluded from the analysis ($n = 35$).

Strain analysis involved the readers to set three markers on two orthogonal apical views, namely, two markers at the edges of the mitral valve ring and one marker at the LV apex. The LV endocardial border was then automatically detected by the 3D WM tracking software (Toshiba Medical Systems), after which the reader could manually adjust the endocardial border and myocardial thickness if necessary. The system then automatically performed the strain analysis through the entire cardiac cycle, providing continuous values of global and segmental strains for all 16 segments simultaneously. The measurement of global strain is comparable to other global functional measurements such as LV EF, whereas segmental strain is a quantitative measurement of the regional function of the different segments of the left ventricle that is comparable to the qualitative visual assessment of segmental wall motion.

Studied echocardiographic parameters included LV volumes, mass, EF, as well as global and segmental measurements of circumferential, longitudinal, radial, and area strains. Measurements were taken in accordance with the recommendations for chamber quantification of the American Society of Echocardiography.[15]

Inter- and intra-observer reliability

Observer reliability of global and segmental strains was assessed in 50 random healthy subjects in a blinded fashion as part of previously performed reliability studies that also included patients.[5,7] Datasets were analysed for inter-observer reliability by two separate observers. Intra-observer measurements were performed on average 1 week apart in a random order.

Statistical analysis

Data were analysed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). Continuous data are presented as mean ± standard deviation (SD). Categorical data are presented as a count and percentage. Normal distribution of variables was verified using the Kolmogorov–Smirnov test. Comparisons between subjects were made with the independent sample *t*-test or analysis of variance (ANOVA) as appropriate. Comparisons between segments were performed with ANOVA with a repeated-measures design. Statistical significance was defined as a probability value of <0.05. Reliability was assessed using the standard error of measurement (SEM) as a parameter of absolute measurement error expressed in the unit of measurement as well as the relative standard error (RSE) expressed in percentage.

Results

Population characteristics

A total of 303 healthy subjects were included in the study in approximately equal proportions of predefined age groups: 18–30 years ($n = 65$; 52% men), 31–40 years ($n = 59$; 54% men), 41–50 ($n = 60$; 48% men), 51–60 years ($n = 58$; 50% men), and >60 years of age ($n = 61$; 52% men). Overall, the healthy subjects were 42 ± 14 years old (range 18–82 years) and 51% were men. A total of 794 segments (16%) were excluded due to inadequate image quality or persistent poor tracking. The anterior wall was the region most often poorly visualized. *Table 1* summarizes measurements of volumetric chamber indices and myocardial deformation indices for all healthy subjects. All strain parameters demonstrated a normal distribution. Circumferential, longitudinal, and area strains also had small SDs, indicating relatively tight normal ranges, whereas normal ranges of radial strain were quite broad.

Normal reference values stratified according to gender and age

Unlike radial and circumferential strains, which were comparable between both genders, longitudinal and area strains were somewhat higher in magnitude in women than in men (*Table 1* and *Figure 1*). Except for longitudinal strain, all strains increased with age up to the sixth decade, after which strains appeared to decrease again. In contrast, longitudinal strain gradually decreased with age (*Table 2* and *Figure 2*). These gradual changes in the mean strain between different age groups were significant for all strains.

Functional non-uniformity

Table 3 demonstrates the functional non-uniformity found in the normal LV for all strains. The average value of strain differed significantly between individual segments as well as between different walls and levels of the LV. In the circumference, radial strain demonstrated the most non-uniformity in the circumference of the LV with

Table 1 Normal values of echocardiographic variables for all healthy subjects and stratified according to gender

Variable	All (*n* = 303)	Men (*n* = 156)	Women (*n* = 147)	*P*-value (gender)
Volumetric				
EDV (mL)	110 ± 20	118 ± 22	103 ± 15	<0.001
ESV (mL)	44 ± 10	47 ± 11	40 ± 8	<0.001
SV (mL)	67 ± 11	71 ± 12	63 ± 9	<0.001
EF (%)	61 ± 3	60 ± 3	61 ± 3	0.02
Mass (g)	118 ± 19	125 ± 19	109 ± 16	<0.001
Global strain				
Radial (%)	35.6 ± 10.3	35.2 ± 9.5	35.9 ± 11.0	0.58
Circumferential (%)	−30.6 ± 2.6	−30.5 ± 2.5	−30.6 ± 2.7	0.63
Longitudinal (%)	−15.9 ± 2.4	−15.5 ± 2.4	−16.3 ± 2.3	0.003
Area (%)	−42.0 ± 2.4	−41.7 ± 2.5	−42.4 ± 2.2	0.01
Segmental strain				
Radial (%)	35.4 ± 17.5	35.1 ± 17.1	35.7 ± 17.9	0.31
Circumferential (%)	−30.5 ± 6.0	−30.5 ± 5.9	−30.6 ± 6.1	0.63
Longitudinal (%)	−15.9 ± 6.0	−15.4 ± 6.0	−16.4 ± 6.0	<0.001
Area (%)	−42.0 ± 6.7	−41.7 ± 6.7	−42.4 ± 6.7	0.001

EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction.

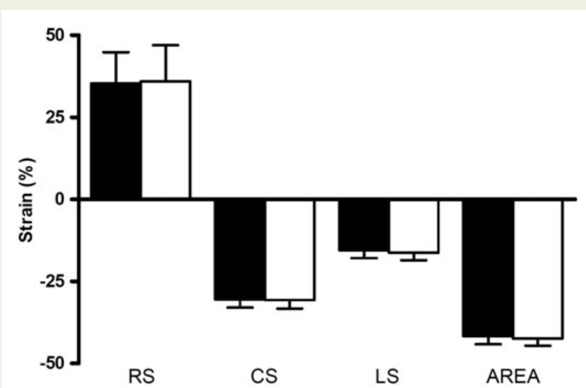

Figure 1 Differences in the magnitude of strain between men and women. Black columns represent men and white columns depict women.

significantly increasing strain values from the inferior to the anterior wall ($P < 0.001$). Non-uniformity between different levels of the LV was very heterogeneous between the different strain parameters. In general, normal values of circumferential and area strains were most consistent with only marginally differences found between different segments, walls, and levels.

Inter- and intra-observer reliability

Reliability of global and segmental strains are given in *Table 4*. As expected, the intra-observer reliability of strain measurements was superior to the inter-observer reliability. Furthermore, the reliability of global strain measurements was generally superior to that of segmental measurements for all strain parameters.

Discussion

The current study establishes the normal ranges of global and segmental LV strain using 3DSTE for clinical use. It demonstrates differences found between men and women, different age groups, as well as the functional non-uniformity of the normal LV. These findings are important, because they may demonstrate the necessity for gender-, age-, and/or segment-specific normal ranges.

Multiple studies have evaluated normal strain values with 2D speckle tracking echocardiography (2DSTE), showing a wide reference range of LV strain in apparently normal subjects.[16] Moreover, studies have demonstrated discordant results between 2DSTE and 3DSTE, which may be explained by the 3D cardiac motion that is partly lost when imaging in two dimensions.[3,4,17] Longitudinal and radial strains by 3DSTE are significantly smaller than by 2DSTE, whereas circumferential strain is significantly larger using 3DSTE. Only three studies have previously reported normal reference values of either directional strains or area strain using 3DSTE in small samples of healthy adult subjects.[4,5,18] This is the first multicentre study determining normal ranges of all LV strain parameters using 3DSTE in a large healthy adult Caucasian population with a broad range in age. Similar to previous 2DSTE and 3DSTE studies, it demonstrates relatively tight normal ranges for circumferential, longitudinal, and area strains, but a wide reference range for radial strain. The difficulty in estimating radial strain is not unique to 3DSTE and has been demonstrated previously with 2DSTE.[19] It is likely related to the fact that radial strain must be calculated over a relatively small region due to the limited wall thickness, in combination with limited spatial resolution in the radial direction. However, when assuming that myocardial volume is conserved during the cardiac cycle, radial strain could also be estimated as the negative of area strain, which would improve its measurement accuracy considerably.[20] Finally, it

Table 2 Normal values of LV strain stratified according to the age group

Variable	18–30 years (*n* = 65)	31–40 years (*n* = 59)	41–50 years (*n* = 60)	51–60 years (*n* = 58)	61–82 years (*n* = 61)	*P*-value
Global strain						
Radial (%)	33.4 ± 9.3	33.7 ± 8.6	35.6 ± 11.1	38.1 ± 9.7	37.3 ± 11.8	0.04
Circumferential (%)	−29.3 ± 2.0	−29.7 ± 2.4	−31.0 ± 2.5	−31.7 ± 2.4*	−31.2 ± 2.8	<0.001
Longitudinal (%)	−16.5 ± 2.1**	−16.1 ± 2.1	−15.7 ± 2.8	−15.6 ± 2.2	−15.3 ± 2.5	0.04
Area (%)	−41.5 ± 2.1	−41.5 ± 2.1	−42.4 ± 2.6	−42.9 ± 2.2	−42.1 ± 2.6	0.005
Segmental strain						
Radial (%)	33.2 ± 17.4	33.3 ± 17.0	35.9 ± 17.3	37.8 ± 17.5	37.2 ± 18.0	<0.001
Circumferential (%)	−29.3 ± 5.7	−29.6 ± 5.7	−31.1 ± 6.1	−31.7 ± 5.9	−31.2 ± 6.3	<0.001
Longitudinal (%)	−16.5 ± 5.7	−16.1 ± 5.9	−15.8 ± 6.1	−15.7 ± 6.1	−15.3 ± 6.1	<0.001
Area (%)	−41.4 ± 6.5	−41.4 ± 6.5	−42.4 ± 6.9	−42.9 ± 6.7	−42.0 ± 7.2	<0.001

*$P < 0.01$ compared with age groups 18–30 years and 31–40 years of age.
**$P = 0.02$ compared with age group 61–82 years of age.

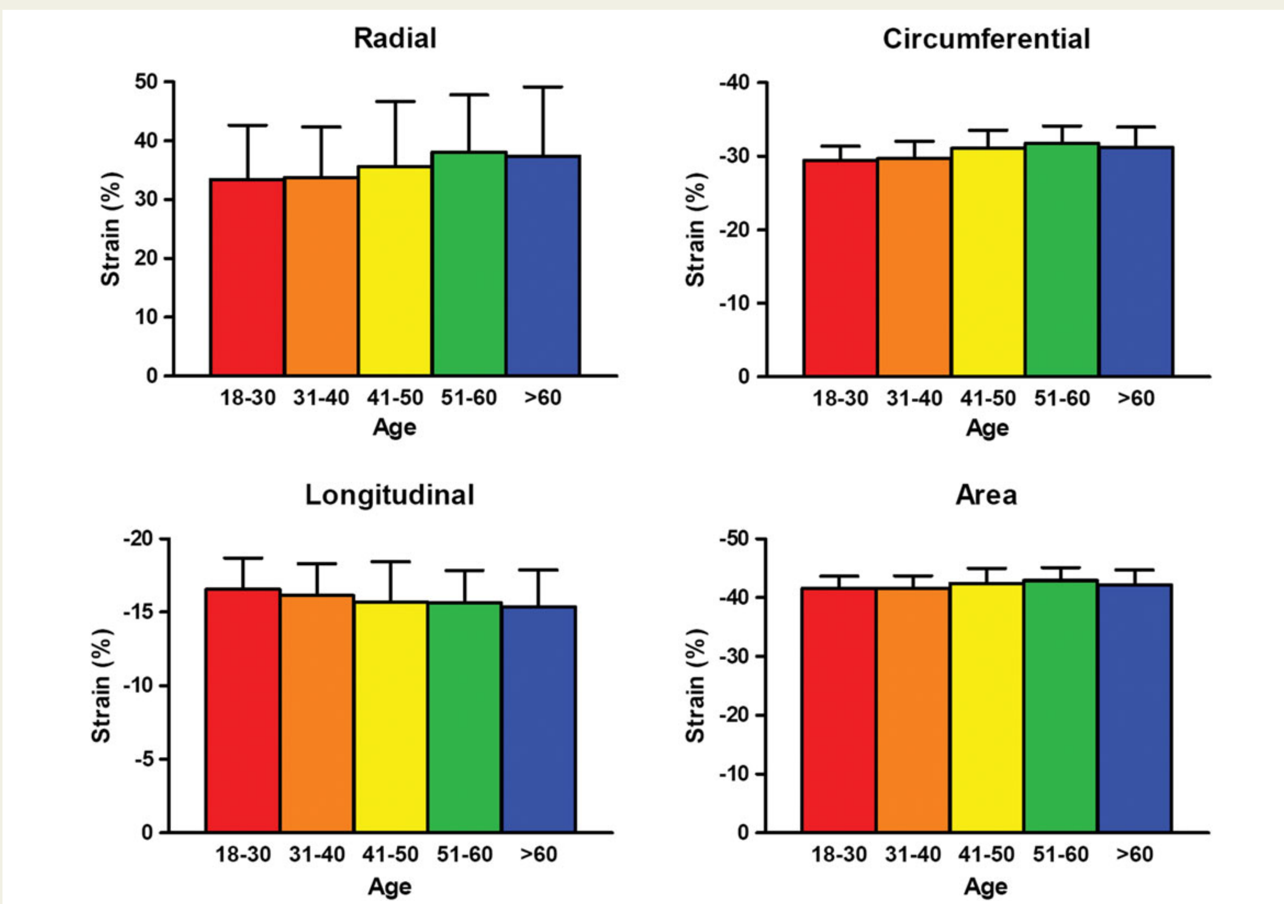

Figure 2 Differences in the magnitude of strain between different age groups.

is clear from the results from the current study that normal LV strain values with 3DSTE are notably different from previously reported normal values using 2DSTE and should therefore not be used interchangeably.[21]

Gender and age

Large differences between men and women in LV volumes, mass, and to a lesser extent EF have been well established, regardless of used echocardiographic imaging modality.[15,22,23] Data on differences in

Table 3 Comparisons of normal segmental values of LV strain

	All levels	Basal	Mid	Apical	*P*-value (levels)
Radial strain (%)					
All walls	35.4 ± 17.5	34.8 ± 17.8	38.5 ± 18.2	31.5 ± 15.2	<0.001
Anterior	40.4 ± 18.2	40.2 ± 18.1	46.1 ± 18.6	34.8 ± 14.2	0.001
Anteroseptal	38.1 ± 17.0	39.8 ± 18.1	42.4 ± 16.8	32.4 ± 14.4	0.09
Inferoseptal	33.0 ± 15.3	32.3 ± 16.0	34.2 ± 15.4	32.4 ± 14.4	0.16
Inferior	27.4 ± 15.9	27.9 ± 16.6	28.8 ± 16.1	25.4 ± 14.9	0.54
Inferolateral	33.8 ± 16.6	32.1 ± 15.5	36.1 ± 18.2	33.0 ± 15.7	0.008
Anterolateral	38.1 ± 17.6	37.5 ± 17.3	43.7 ± 18.0	33.0 ± 15.7	<0.001
P-value (walls)	<0.001	<0.001	<0.001	<0.001	–
Circumferential strain (%)					
All walls	−30.5 ± 6.0	−29.6 ± 6.3	−31.4 ± 5.7	−30.5 ± 5.9	<0.001
Anterior	−29.2 ± 5.8	−28.7 ± 5.9	−30.7 ± 5.5	−28.0 ± 5.5	<0.001
Anteroseptal	−31.2 ± 6.0	−29.7 ± 6.2	−32.4 ± 6.0	−31.4 ± 5.7	<0.001
Inferoseptal	−31.0 ± 6.2	−29.6 ± 6.7	−31.8 ± 6.0	−31.4 ± 5.7	<0.001
Inferior	−31.4 ± 5.7	−30.5 ± 6.1	−31.5 ± 5.5	−32.1 ± 5.4	0.054
Inferolateral	−30.3 ± 6.0	−29.6 ± 6.3	−31.0 ± 5.5	−30.4 ± 6.1	0.01
Anterolateral	−30.2 ± 6.1	−29.2 ± 6.5	030.9 ± 5.6	−30.4 ± 6.1	0.001
P-value (walls)	0.004	0.055	0.007	<0.001	–
Longitudinal strain (%)					
All walls	−15.9 ± 6.0	−16.9 ± 6.6	−14.9 ± 5.2	−16.0 ± 6.1	<0.001
Anterior	−15.2 ± 6.7	−19.9 ± 6.6	−15.0 ± 5.9	−11.6 ± 4.7	<0.001
Anteroseptal	−16.0 ± 5.5	−14.6 ± 6.0	−15.8 ± 4.9	−17.6 ± 5.3	0.01
Inferoseptal	−15.8 ± 5.4	−14.1 ± 5.6	−15.4 ± 4.7	−17.6 ± 5.3	0.004
Inferior	−16.6 ± 5.8	−16.2 ± 5.8	−14.5 ± 4.8	−19.3 ± 5.6	<0.001
Inferolateral	−15.5 ± 6.0	−17.2 ± 6.5	−13.7 ± 5.2	−15.6 ± 5.7	<0.001
Anterolateral	−16.9 ± 6.3	−20.3 ± 6.3	−15.2 ± 5.6	−15.6 ± 5.7	<0.001
P-value (walls)	<0.001	<0.001	<0.001	<0.001	–
Area strain (%)					
All walls	−42.0 ± 6.7	−41.5 ± 7.0	−42.2 ± 6.3	−42.4 ± 7.1	0.005
Anterior	−40.4 ± 6.8	−43.1 ± 6.7	−41.5 ± 6.3	−37.0 ± 6.0	0.01
Anteroseptal	−43.1 ± 6.8	−39.9 ± 6.9	−44.5 ± 6.0	−44.6 ± 6.5	<0.001
Inferoseptal	−42.3 ± 6.9	−39.4 ± 7.1	−42.7 ± 6.2	−44.6 ± 6.5	<0.001
Inferior	−43.1 ± 6.4	−41.9 ± 6.4	−41.8 ± 6.1	−45.7 ± 6.0	0.80
Inferolateral	−41.5 ± 6.5	−41.7 ± 7.0	−40.8 ± 6.0	−42.1 ± 6.5	0.14
Anterolateral	−42.5 ± 6.7	−43.7 ± 7.0	−41.7 ± 6.3	−42.1 ± 6.5	0.001
P-value (walls)	<0.001	<0.001	<0.001	<0.001	–

the magnitude of LV strain between healthy men and women have been lacking up until now. The current study demonstrates no large gender differences in LV strain. Although statistically significant differences were found for longitudinal and area strains, these differences seem clinically irrelevant and do not necessitate separate gender-specific cut-off values. This is in compliance with previous studies performed with 2DSTE that demonstrate only a minor or absent association between LV strain and gender.[16]

Regarding potential differences in LV strain in different age groups, results demonstrate a gradual decrease in longitudinal strain with age, whereas the other LV strains show a variable increase with age up to the sixth decade, after which strains appeared to decrease again. These changes in the magnitude of LV strain with aging, although statistically significant due to the shear number of patients and particularly the number of segments studied in this study, appear to be too small to be clinically relevant for measurement of circumferential, longitudinal, and area strains. For radial strain, the differences were more pronounced, but still reasonably close to the mean not to necessitate age-specific normal values.

Functional non-uniformity

An important observation in the evaluation of this healthy population was differences found in the average value of strain between individual segments, as well as between different walls and levels of the LV. Functional non-uniformity is a known feature of the normal LV that may have consequences for the validity of the assessment of segmental function.[1,3,5,14] Indeed, some differences in the performance measures of segmental wall motion assessment by area

Table 4 Reliability of global and segmental strain measurements

Variable	Intra-observer		Inter-observer	
	SEM	RSE (%)	SEM	RSE (%)
Global strain				
Radial (%)	3.0	8	5.5	15
Circumferential (%)	1.0	3	1.8	6
Longitudinal (%)	0.7	4	1.3	8
Area (%)	1.3	3	2.1	5
Segmental strain				
Radial (%)	6.1	17	10.1	28
Circumferential (%)	2.5	8	3.6	12
Longitudinal (%)	1.9	12	3.4	21
Area (%)	3.4	8	4.6	11

SEM, standard error of measurement; RSE, relative standard error.

strain were previously observed between different LV levels, although none were substantial enough to warrant separate cut-off values.[5] In the current study, the general consistency in the magnitude of segmental area strain seems to confirm these previous findings. In addition, circumferential strain demonstrated very consistent strain values between different segments, walls, and levels. However, radial strain increases considerably from the inferior to the anterior wall and shows higher mean values in the mid-ventricular wall compared with the base and apex. In contrast, longitudinal strain was lower in the mid-ventricular wall compared with the basal and apical levels, as previously noted in an analysis of normal segments in patients.[3] Moreover, there is considerable heterogeneity in mean longitudinal strain between individual segments. The apical anterior wall, in particular, demonstrated a surprisingly low mean strain value compared with other segments, which may in part be due to the known difficulty with adequate visualization and tracking of this particularly challenging area of the LV. However, even when this segment is excluded, the absolute and relative mean differences found between the remaining LV segments for segmental longitudinal strain can still add up to almost 7 and 50%, respectively. For these reasons as well as the relatively large SD to mean ratio of segmental radial and longitudinal strains, segment-specific cut-off values are warranted for these strain parameters for adequate distinction between what is normal and what should be considered pathological, particularly if diagnostic or therapeutic decisions are based on their assessment. Overall, circumferential and area strains demonstrate the most consistent normal ranges. Previous studies have also shown their reproducibility to be superior to that of radial and longitudinal strains.[5,7] Ultimately, clinical studies will determine whether 3DSTE-derived LV strain parameters have a value for diagnosis and prognosis of heart disease in clinical practice.

Limitations

Some patient (race, ethnicity, and anthropometry) and haemodynamic (blood pressure) parameters were not taken into account during the present study. However, some previous studies have demonstrated limited contributions of these factors to the variability of myocardial deformation.[14,16]

Furthermore, the software used does not provide an automated measure of tracking quality. Segments were evaluated on interpretability based on image quality after acquisition and before analysis, as preordained in the study protocol. Thus, it may be possible that segments were excluded from analysis that would have been accurately tracked and analysed by the 3DSTE software despite poor image quality. *Vice versa*, it is likely that segments were included in the analysis that were inadequately tracked and analysed despite the image quality being deemed adequate.

Finally, the current study was performed with equipment of only one vendor, i.e. Toshiba Medical Systems. Previous studies have demonstrated high inter-vendor inconsistency in reference values.[24,25] The established normal ranges are not applicable to data derived with analysis software by other vendors and consequently similar research using other vendors' equipment is necessary.[26] Currently, a similar large prospective multicentre study is being performed, which will provide normal ranges of LV strain using 3DSTE equipment by three other vendors.[27] These studies will help improve standardization of software algorithms and the manner in which clinicians perform and interpret their measurement results.

Conclusions

Normal ranges of global and segmental LV strain using 3DSTE have been established for clinical use. Differences in the magnitude of LV strain are present between men and women as well as between different age groups. Moreover, there are differences between different segments, walls, and levels as part of the functional non-uniformity of the normal LV that necessitate the use of segment-specific normal ranges for radial and longitudinal strains. Circumferential and area strains demonstrate the most consistent normal ranges overall.

Conflict of interest: none declared.

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