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Normal Values of Left Ventricular Longitudinal and Circumferential Layer-Specific Strain: A Meta-Analysis

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Abstract

Background: Layer-specific strain is a relatively recent tool that is supposed to improve myocardial deformation assessment. Although it has been used to explore various cardiovascular diseases, there is no recommendation to use this tool in clinical practice. Moreover, there are few data concerning normal values of layer-specific strain in healthy individuals. Our aim was to perform a meta-analysis to determine normal ranges of longitudinal and circumferential layer-specific strain values and define factors that could influence layer-specific strain normal values. **Methods:** We searched Medline, Embase and Cochrane database using the following code: (((layer specific[Title/Abstract] OR multilayer[Title/Abstract])) AND (Strain[Title/Abstract] OR speckle tracking[Title/Abstract])) AND echocardiography[Title/Abstract], completing this search on May, 2019. All studies reporting left ventricular longitudinal or circumferential layer-specific strain (endocardial, mid-myocardial and epicardial) in healthy normal subjects were included. **Results:** 869 subjects from 18 studies were included. Normal values for longitudinal layer-specific strain at endocardial, mid-myocardial, and epicardial layer were respectively when considering EchoPAC software: −23.90 ± 0.62, −23.90 ± 0.62, −18.10 ± 1.54; Toshiba software: −15.73 ± 0.92, −15.73 ± 0.92, −12.06 ± 0.30 and VVI software: −19.10 ± 1.30, −19.09 ± 1.30, −10.80 ± 1.00. Circumferential endocardial, mid-myocardial and epicardial layer-specific strain normal values were for EchoPAC software: −31.74 ± 1.56, −22.84 ± 0.90, −17.15 ± 1.30. There was only one study for VVI and Toshiba software. There was a gradient between endocardial and epicardial strain with layer-specific strain decreasing from endocardial to epicardial layer. Main limit of reproducibility of this tool was intervendor variability. **Conclusion:** Normal ranges of layer-specific strain (longitudinal and circumferential) are provided in this meta-analysis according to 3 vendors: EchoPAC, Toshiba and VVI. Layer-specific strain decreases from the endocardial

to the epicardial layer in both longitudinal and circumferential strain. Main cause of variability was the intervendor variability in monolayer strain. Effort for standardization between vendors should be required.

Keywords

Echocardiography, Layer Specific, Multilayer Strain, Speckle Tracking

1. Background

Assessment of left ventricle (LV) function using global longitudinal strain (GLS) is recommended in cancer patients receiving chemotherapy at risk of cardiotoxicity (anthracycline, trastuzumab). Normal value of LV GLS using speckle tracking tool is −20% [1]. However, it has been recognized that this tool could suffer from different factors of variability as: age, sex, and systolic arterial pressure [2] [3]. Effort to standardized method to define strain assessment has been performed with consensus between industrials and clinicians [4].

Layer-specific strain (LSS) is a relatively recent tool that is supposed to improve myocardial deformation assessment. It provides evaluation of myocardial deformation in three layers: endocardial, mid-myocardial and epicardial using speckle tracking. It has been tested in various conditions, such as myocardial ischemia [5]-[11], presence of cardiovascular risk factors [12]-[15], and cardio-oncology [16] [17]. Nevertheless, there is no recommendation to use LSS in clinical practice. There are few data concerning normal values of layer-specific strain in healthy individuals, which must be required before being able to preconize widespread of this technique. As found for monolayer strain, LSS may present various parameters that could influence the measurement of strain, including features specific to patients: age, sex, hemodynamic factors, and specific to the technology with an intervendor variability [18]. The routine application of LSS in clinical practice requires to define normal ranges and knowledge of main causes of variability.

The objective of this study was to perform a meta-analysis to determine normal ranges of longitudinal and circumferential LSS and define main factors of variability of these measurements.

2. Methods

We performed a wide research in Medline, Embase and Cochrane database using the following code: (((layer specific[Title/Abstract] OR multilayer[Title/Abstract])) AND (Strain[Title/Abstract] OR speckle tracking[Title/Abstract])) AND echocardiography[Title/Abstract] completing this search on May, 2019.

All articles were selected by two operators independently (YA, AM) and when they were discordant, they ended up at a consensus.

Studies were included if it provided LV LSS using two-dimensional speckle-tracking echocardiography in healthy normal subjects, either in the control group or as

the main objective of the study.

Only human studies written in English were assessed for inclusion. Furthermore, the reference lists of these articles were scrutinized to further identify studies pertinent to the topic. All studies that reported LV longitudinal or circumferential layer-specific strain: endocardial (endo), mid-myocardial (mid) and epicardial (epi) in healthy normal subjects were included.

Studies that were excluded had the following criteria: use of 2-layer-specific strain (endocardial, epicardial) without assessment of mid-myocardial layer, no evaluation in human subjects, inclusion of children, assessment of right ventricular strain, case report or review, abstracts without full text, editorial comments, and letters to the editor.

Clinical, echocardiographic, and strain data were extracted from individual studies by one author (AM), verified by a second (YA) and entered into an electronic database. Mean and standard deviations for longitudinal and circumferential LSS were extracted from the text and tables.

Data recorded in a database were: author, years of publication, sex, age, heart rate, systolic arterial pressure, body mass index, and values of longitudinal and circumferential LSS of each layer from healthy control group.

The search strategy, study selection and analysis adhered to PRISMA Guidelines [19].

Statistical Analysis

The overall means and 95% CIs of longitudinal and circumferential LSS were computed using fixed-effects models with inverse variance weighting as pooling method. Between-study heterogeneity was assessed by measuring inconsistency (I^2, the percentage of total variance across studies attributable to heterogeneity of results rather than chance). We performed a fixed-effects meta-regression for variables suspected to influence strain to assess their effect on normal LSS variation, such as the mean age of patients in studies and the software used. Statistical analysis was performed using standard and metafor packages in R software 4.0.3 with two-tailed tests and p-values < 0.05 considered as significant.

3. Results

3.1. Study Selection

A total of 95 titles were screened and 18 studies were included in this meta-analysis. Therefore, 869 patients were included in this analysis. **Figure 1** presents the flow chart for the selection of studies and the reasons for exclusion of others. **Table 1** presents main demographic and clinical characteristics of the population. 17 studies analyzed longitudinal LSS, and 10 circumferential LSS.

3.2. Normal Ranges

Longitudinal LSS

Normal values for longitudinal LSS are presented in **Table 2**. When considering

EchoPAC software, longitudinal endocardial, mid-myocardial and epicardial LSS were respectively: −23.90 ± 0.62, −23.90 ± 0.62, −18.10 ± 1.54. When considering Toshiba software, longitudinal endocardial, mid-myocardial and epicardial LSS were respectively −15.73 ± 0.92, −15.73 ± 0.92, −12.06 ± 0.30. When considering VVI software, longitudinal endocardial, mid-myocardial and epicardial LSS were respectively −19.10 ± 1.30, −19.09 ± 1.30, −10.80 ± 1.00.

Circumferential LSS

When considering Circumferential LSS, only values obtained with EchoPAC software were summarized in Table 2 because there was only one study respectively for Toshiba and VVI software that analyzed the circumferential LSS.

When considering EchoPAC software, circumferential endocardial, mid-myocardial and epicardial LSS were respectively −31.74 ± 1.56, −22.84 ± 0.90, −17.15 ± 1.30. When considering Toshiba software, circumferential endocardial, mid-myocardial and epicardial LSS were respectively −24.3 ± 3.3, −13.3 ± −2.5, 8.6 ± 2.3 [20]. When considering VVI software, circumferential endocardial, mid-myocardial and epicardial LSS were respectively −18.8 ± 5.1, −13.1 ± 3.6, −8.8 ± 2.7 [21].

Strain values are higher in EchoPAC than in VVI and Toshiba regardless of the type of strain (endocardial, mid-myocardial, epicardial).

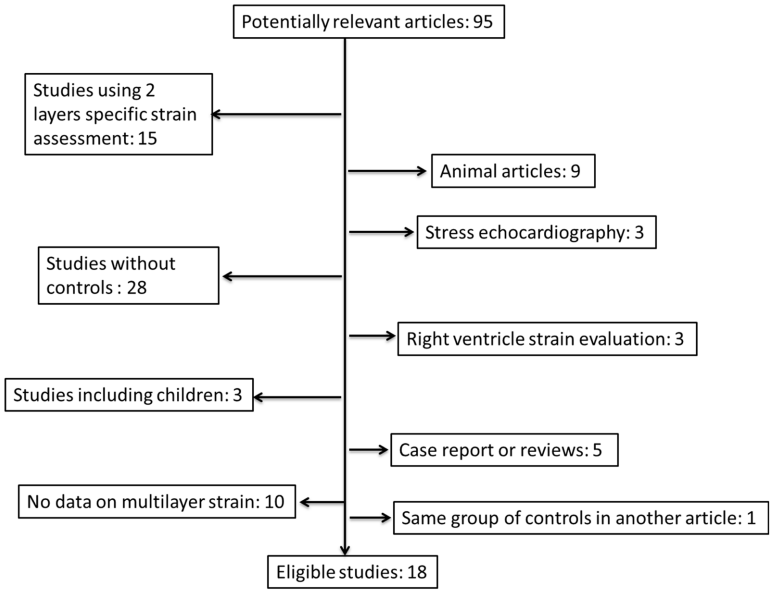

Figure 1. Study design. Flow chart presenting the selection process for published reports.

Table 1. Characteristics of the study population.

Author/Years	n	Sex Female n (%)	Age (Years)	BMI	PAS (mmHg)	HR	LVEF
Bogdanović *et al*., 2019 [28]	20	12 (60)	36.2 ± 2	23.8 ± 0.7	NA	NA	65.1 ± 0.4
Ozkaramanli Gur *et al*., 2018 [21]	30	13 (43.3)	38.5 ± 9.9	25.1 ± 3.9	118 ± 15.7	75.5	63.8 ± 4.2
Sun *et al*., 2019 [29]	80	17 (21.2)	50.8 ± 12.4	NA	121.8 ± 10.5	70 ± 10.7	65 ± 6.4

Continued

Xu *et al.*, 2018 [14]	67	NA	NA	21.3 ± 2.3	NA	67 ± 11	65 ± 6
Kang *et al.*, 2018 [17]	27	15 (55.6)	50.4 ± 13.4	NA	124.8 ± 12.6	78 ± 11.3	66.5 ± 5.6
Abou *et al.*, 2017 [24]	94	40 (42.6)	54 ± 16	25 ± 3.4	NA	NA	62 ± 6.2
Cho *et al.*, 2017 [30]	18	10 (55.6)	60.9 ± 7.19	NA	120 ± 15.8	74 ± 12	65.2 ± 5.5
Tadic *et al.*, 2017 [12]	38	35 (92)	53 ± 8	25.1 ± 3.1	128 ± 8	73 ± 9	64 ± 3
Leng *et al.*, 2017 [15]	32	15 (46.9)	35.6 ± 10.3	NA	118 ± 11.6	68.6 ± 6.6	66 ± 2.8
Tadic *et al.*, 2018 [31]	44	22 (50)	52 ± 8	26.4 ± 2.2	127 ± 9	68 ± 6	65 ± 4
Cong *et al.*, 2016 [32]	30	30 (100)	28.2 ± 6.6	NA	104.2 ± 10.7	81 ± 14	67.6 ± 5.1
Kim *et al.*, 2016 [13]	31	12 (38.7)	62.5 ± 8.7	24.7 ± 3.2	126 ± 13	NA	63.5 ± 5.9
Wang *et al.*, 2016 [33]	44	22 (50%)	55.5 ± 8.4	NA	126.8 ± 14.6	68.7 ± 7.5	64.5 ± 4.4
Shi *et al.*, 2016 [25]	119	60 (50.4)	48 ± 9.3	23.5 ± 2.9	110.2 ± 12.9	66 ± 9.6	63.4 ± 2.9
Okada *et al.*, 2015 [20]	27	12 (44.4)	53 ± 9.7	NA	119.4 ± 12.2	67 ± 11	65 ± 4.2
Cadeddu *et al.*, 2014 [34]	18	18 (100)	52 ± 5.3	25.6 ± 3.2	128 ± 11	75 ± 13	67 ± 9.2
Bachner-Hinenzon *et al.*, 2010 [35]	120	NA	NA	NA	NA	69 ± 1.1	61 ± 0.7
Adamu *et al.*, 2009 [5]	30	10 (33.3)	60.5 ± 16.5	NA	NA	NA	59 ± 3.2

BMI: Body mass index; HR: Heart rate; LVEF: Left ventricle ejection fraction. NA means not available (non-disponible in French).

Table 2. Normal values of longitudinal and circumferential layer-specific strain according to vendor considering 3 layers.

			Longitudinal LSS			
Layer	Endo	I^2	Mid	I^2	Epi	I^2
EchoPAC	23.90 ± 0.62	98.90	23.90 ± 0.62	98.90	18.10 ± 1.54	99.89
VVI	19.10 ± 1.30	94.86	19.09 ± 1.30	94.86	10.80 ± 1.00	93.77
Toshiba	15.73 ± 0.92	92.63	15.73 ± 0.92	92.63	12.06 ± 0.30	0.00
			Circumferential LSS			
Layer	Endo	I^2	Mid	I^2	Epi	I^2
EchoPAC	31.74 ± 1.56	98.34	22.84 ± 0.90	96.61	17.15 ± 1.30	98.60

Endo: Endocardial; Mid: Mid-myocardial; Epi: Epicardial.

3.3. Factors Associated with Layer-Specific Strain Normal Values

A large part of the heterogeneity was thus explained by the vendor.

Due to the lack of data in various studies, the other potential variability factors of layer-specific strain were not studied. We limited ourselves to the study of correlations between LSS and different clinical and echocardiography characteristics.

Longitudinal layer-specific strain (Table 3):

Factors associated with longitudinal LSS for endocardial layer were: Body mass index (BMI), Body surface area (BSA), LVEF and vendors. Factors associated with longitudinal LSS for mid-myocardial layer were: BMI, BSA, LVEF and vendors. Factors associated with longitudinal LSS for epicardial layer were: BSA, LVEF and vendors.

Circumferential layer-specific strain (Table 4):

Factors associated with circumferential LSS for endocardial layer were: Female

gender, BSA and vendors. Factors associated with circumferential LSS for mid-myocardial layer were: Age, heart rate and vendors. Factors associated with circumferential LSS for epicardial layer were: age, heart rate, systolic blood pressure and vendors.

Table 3. Factors associated with longitudinal layer-specific strain values considering all vendors (meta-regression).

Factors	Endocardial Layer		Mid-Myocardial Layer		Epicardial Layer	
	CC	p	CC	p	CC	p
Female gender	0.22 ± 2.02	0.91	−0.39 ± 1.54	0.80	−0.60 ± 1.34	0.66
Age	−0.06 ± 0.04	0.18	−0.03 ± 0.03	0.28	−0.03 ± 0.03	0.31
BMI	−0.71 ± 0.26	**0.01**	−0.49 ± 0.21	**0.02**	−0.34 ± 0.19	0.08
BSA	−7.69 ± 2.97	**0.01**	−5.91 ± 2.34	**0.01**	−4.52 ± 2.35	**0.05**
HR	0.05 ± 0.10	0.64	0.03 ± 0.11	0.77	0.05 ± 0.15	0.71
LVEF	0.59 ± 0.22	**0.01**	0.76 ± 0.21	**0.00**	1.04 ± 0.26	**<0.001**
SBP	−0.02 ± 0.06	0.73	−0.01 ± 0.05	0.76	−0.01 ± 0.04	0.74
DBP	0.05 ± 0.10	0.59	0.03 ± 0.08	0.64	0.05 ± 0.06	0.46
Toshiba software	−8.17 ± 1.36	**<0.0001**	−6.72 ± 1.35	**<0.0001**	−5.94 ± 1.73	**0.0006**
VVI software	−4.80 ± 1.37	**0.0004**	−6.08 ± 1.33	**<0.0001**	−7.29 ± 1.72	**<0.0001**

BMI: Body mass index; BSA: Body surface area; HR: Heart rate; LVEF: Left ventricle ejection fraction; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Table 4. Factors associated with circumferential layer-specific strain values considering all vendors (meta-regression).

Factors	Endocardial Layer		Mid-Myocardial Layer		Epicardial Layer	
	CC	p	CC	p	CC	p
Female gender	−14.4 ± 6.12	**0.02**	−4.64 ± 5.00	0.35	0.13 ± 6.89	0.98
Age	0.17 ± 0.23	0.46	0.37 ± 0.11	**0.0005**	0.52 ± 0.12	**<0.0001**
BMI	−0.74 ± 0.76	0.33	0.26 ± 0.15	0.08	0.71 ± 0.65	0.28
BSA	−20.28 ± 9.47	**0.03**	−5.12 ± 5.23	0.33	−0.74 ± 9.23	0.94
HR	0.39 ± 0.35	0.27	0.50 ± 0.15	**0.0013**	0.65 ± 0.22	**0.003**
LVEF	−0.72 ± 0.68	0.29	−0.72 ± 0.47	0.12	−0.95 ± 0.57	0.10
SBP	−0.33 ± 0.23	0.15	0.20 ± 0.14	0.15	0.48 ± 0.13	**0.0002**
DBP	−0.29 ± 0.52	0.58	−0.15 ± 0.32	0.63	−0.12 ± 0.44	0.77
Toshiba software	−7.43 ± 4.39	**0.09**	−9.56 ± 2.87	**0.0009**	−8.54 ± 3.75	**0.02**
VVI software	−12.93 ± 4.44	**0.0036**	−9.76 ± 2.90	**0.0008**	−8.34 ± 3.75	**0.03**

BMI: Body mass index; BSA: Body surface area; HR: Heart rate; LVEF: Left ventricle ejection fraction; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

3.4. Gradient

There is a gradient between endocardial and epicardial strain. For both longitudinal and circumferential LSS, normal value decreases from the endocardial to epicardial layer.

4. Discussion

To our knowledge, this study is the first meta-analysis that aimed to define longitudinal and circumferential LSS. Main results were as follows: When considering EchoPAC software, normal values for longitudinal LSS were −23.90 ± 0.62 (endo), −23.90 ± 0.62 (mid), −18.10 ± 1.54 (epi). When considering Toshiba software, normal values for longitudinal LSS were −15.73 ± 0.92 (endo), −15.73 ± 0.92 (mid), −12.06 ± 0.30 (epi). When considering VVI software, normal values were −19.10 ± 1.30 (endo), −19.09 ± 1.30 (mid), −10.80 ± 1.00 (epi). Circumferential endocardial, mid-myocardial and epicardial layer-specific strain for EchoPAC software were respectively −31.74 ± 1.56, −22.84 ± 0.90, and −17.15 ± 1.30. There is a gradient between endocardial and epicardial strain. Longitudinal and circumferential LSS decrease from the endocardial to epicardial layer.

Layer-specific strain normal values:

Few studies have aimed to specifically define normal range of longitudinal and circumferential LSS in healthy individuals. Furthermore, for this work we only included studies which consider 3 layers (endo, mid, epi) and excluded those considering only two layers [22] [23].

Shi *et al*. performed a prospective observational study with aim to define reference value of both longitudinal and circumferential LSS and investigate the impact of age, gender, and other physiologic factors. Results revealed a gradient of strain with a value of LSS decreasing from endocardial to epicardial layer. Mean global longitudinal strain in the endocardial layer, in the mid-myocardial layer and in the epicardial layer were −24.3% ± 3.1%, −21.3% ± 2.9%, and −18.9% ± 2.8%, respectively. Mean global circumferential strain in the endocardial layer, in the mid-myocardial layer and in the epicardial layer were −34.3% ± 4.4%, −20.5% ± 3.0%, and −11.8% ± 2.7%, respectively. In an observational study, Abou *et al*. specify influence of increasing age on variation of longitudinal and circumferential LSS normal values. Their results demonstrated that with increasing age, the magnitude of LV longitudinal strain at the basal level declines while the apical LV longitudinal strain increases. Moreover, only presence of diabetes mellitus modulated the effect of age on the LV endocardial layer, and male gender was associated with more impaired longitudinal strain at the epicardial layer [24].

Factors of LSS variability:

Factors of variability described for monolayer strain are: age, sex, systolic arterial pressure and intervendor variability [2] [3]. Takigiku *et al*. [3] found that gender, body surface area and blood pressure were significantly correlated with global longitudinal strain. There was a difference between three vendors. It was advisable to follow-up patients with the same model of machine.

Our results revealed a positive correlation between longitudinal LSS and LVEF and negative correlation with BSA, BMI and vendors. Main cause of variability was intervendor variability.

Shi *et al*. demonstrated that factors which were correlated to longitudinal LSS were: Gender, Heart Rate, and Stroke Volume and Heart Rate was correlated to

circumferential LSS [25].

Intervendor variability must be considered as a limit of LSS reproducibility. In a previous study [18], we assessed intervendor variability by comparing two vendors: Vivid E9TM (General Electric) and the ACUSON SC2000TM (Siemens). 80 patients receiving chemotherapy for cancer were including prospectively and echocardiography were realized by two operators with two types of machine. For a given vendor, strain values decreased from the endocardial layer to the epicardial layer, and strain values obtained with Acuson SC2000 platform were systematically lower than those obtained with Vivid E9 platform ($p < 0.0001$) [18]. In this study, subjects were followed for a cancer, whereas in our study, subjects were normal.

Manovel *et al*. [26] performed 2-D speckle tracking analyses on 28 healthy adult subjects using ultrasound systems and software from GE (General Electric/EchoPAC) and Toshiba. They found a good comparability for global longitudinal strain (between GE and Toshiba), but not for circumferential strain. To explain this difference, the considerable out-of-plane motion of acoustic markers in short-axis views could also represent a limitation for the consistency of findings when transmural and circumferential motion are analysed. In addition, the presence of a transmural deformation gradient and differently oriented myofibril layers within the left ventricular wall should be kept in mind, since the initial position from which myocardial acoustic markers start to be tracked might differ between software.

Takigiku *et al*. [3] highlighted that the contribution of image quality to tracking feasibility differs with vendors. The smallest difference between 3 vendors was noted in the Longitudinal global strain compared to radial and circumferential strain. In addition to the different tracking algorithms used, image quality, post-processing and interpolation techniques, and the computation of the strain, the method of averaging data from the adjacent region and the different weighted averaging computational methods in each of the regions of interest increase the inaccuracies. The different regions of interest between vendors explain partially the different values. The detailed algorithms speckle tracking used in the systems from individual vendors are proprietary and not visible for the user.

In addition, there are multiple definitions of LSS. There is layer-specific strain with 3 layers as in our studies, or 2 layers [22] [23] [27]. This difference in definition of LSS contributes in a certain way to the variability of the values. Normal values for 2-layer-specific strain proposed by Nagata *et al*. were: −23.1 ± 2.3 (endo) and −17.6 ± 1.9 (epi) with EchoPAC software [23]. Alcidi *et al*. found normal values: 25.4 ± 2.1 (endo) and 21.1 ± 1.8 (epi) [22].

Main limits of the study:

Firstly, meta-analysis has inherent limitations: the heterogeneity of the studies, for example, which was important in this study. Secondly, assessment of cause of variability in the measurement of the strain was incomplete because of lack of data. We just studied correlation between different factors, including layer-specific strain,

age, BMI, BSA, HR, blood pressure, LVEF, and type of vendor's model. However, we analyzed normal values per vendor to evaluate differences.

5. Conclusion

This study is the first meta-analysis that defines both longitudinal and circumferential LSS normal ranges considering 3 different vendors: EchoPAC, Toshiba and VVI Software. There is a gradient between endocardial and epicardial strain, in normal subjects, LSS decreases from the endocardial to the epicardial layer. There is an intervendor variability in monolayer strain. Effort for standardization between vendors should be required before recommending widespread use of this tool.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

LV	Left ventricle
LVEF	Left ventricle ejection fraction
GLS	Global longitudinal strain
GCS	Global circumferential strain
LSS	Layer-specific strain
Endo	Endocardial
Mid	Mid-myocardial
Epi	Epicardial
BMI	Body mass index
BSA	Body surface area
VVI	Velocity vector imaging