

Determining the thresholds for abnormal left ventricular strains in healthy subjects by echocardiography: a meta-analysis

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Background: Left ventricular global longitudinal strain (LVGLS), circumferential strain (LVGCS) and radial strain (LVGRS) are echocardiographic parameters with wide clinical applicability. However, the thresholds for abnormal left ventricular (LV) strains, particularly the lower limits of normal (LLN), are not well established. This meta-analysis determined the mean and LLN of two- (2D) and three-dimensional (3D) LV strain in healthy subjects and factors that influence strain measurements.

Methods: We searched PubMed, Embase and Cochrane databases until 31 December 2019 for studies reporting left ventricular (LV) global strain in at least 50 healthy subjects. We pooled means and LLNs of 2D and 3D LV strain using random-effects models, and performed subgroup and meta-regression analysis for LVGLS.

Results: Forty-four studies were eligible totaling 8,910 subjects. The pooled means and LLNs (95% confidence intervals) were -20.1% (-20.7%, -19.6%) and -15.4% (-16.0%, -14.7%) respectively for 2D-LVGLS; -21.9% (-23.4%, -20.3%) and -15.3% (-16.9%, -13.8%) respectively for 2D-LVGCS; and 48.4% (43.8%, 53.0%) and 25.5% (17.8%, 33.1%) respectively for 2D-LVGRS. All pooled analyses demonstrated significant heterogeneity, and means and LLNs of and 3D-LV strains differed marginally from 2D. Only vendor software was associated with differences in pooled means and LLN of 2D-LVGLS.

Conclusions: In conclusion, pooled means and LLNs of 2D- and 3D-LV global strain parameters in healthy subjects were reported. Based on the pooled LLNs, thresholds for abnormal, borderline and normal strains can be defined, such as less negative than -14.7%, between -14.7% and -16.0% and more negative than -16.0% respectively for 2D-LVGLS, and 2D-LVGLS values are only affected by vendor software.

Keywords: Strain; speckle-tracking echocardiography; lower limit of normal (LLN); meta-analysis

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Introduction

Multiple studies have tested the prognostic utility of left ventricular global longitudinal (LVGLS), circumferential (LVGCS) and radial (LVGRS) strains in a wide range of clinical applications, including cardiomyopathies, coronary heart disease and valvular heart disease (1-5). Despite significant investigation, there is no consensus of what constitutes normal variability and what is abnormal strain in an otherwise healthy patient (6,7). Strain measurement variability may stem from biologic variability (e.g., impact of gender, age, body size) or measurement system variability (echocardiographic image quality, software speckle detection, strain calculation). Biologic variability can be resolved by appropriately large, multi-institutional samples of healthy individuals that take into account population diversity. Measurement system variability can be addressed by having a small sample with repeated echocardiographic exams obtained using different ultrasound systems or software. Yet it is close to impossible to perform a study in which both biologic and system variability are assessed.

One way to overcome this problem is to perform a metaanalysis with both biologic and measuring system variability addressed. While meta-analyses of strain measurements have been reported (8-10), they focused on the estimation of the pooled mean of the strain values with corresponding 95% confidence intervals (95% CI) for the mean alone. When determining normal ranges of systolic function parameters in cardiac imaging, such as ejection fraction, fractional area change, tricuspid annular plane systolic excursion and of course strain, the focus is on the threshold at which the value measured becomes abnormally low in magnitude to reflect impaired systolic function, otherwise known as the lower limit of normal (LLN) (7). It is important to note that the 95% CI of the pooled mean by meta-analysis does not accurately reflect the range of normal strain values and does not measure the LLN or its 95% CI, and therefore cannot be used in defining the cut-points for abnormal strain. Our meta-analysis aims to pool the LLNs and update the pooled mean data for two-dimensional (2D-) and three dimensional (3D-) LVGLS, LVGCS and LVGRS by speckle tracking echocardiography in healthy subjects, in order to redefine thresholds of abnormal strains, as well as analyzing baseline parameters that could be associated with left ventricular (LV) strain measurements. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed and presented in the conduct of this metaanalysis, without a separate review protocol.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi. org/10.21037/cdt-20-711).

Methods

Literature search and study selection

PubMed, Cochrane and Embase databases were searched for relevant studies with no restriction on start date until 31 December 2019. The search terms used were (left ventricle) AND (echocardiography) AND (strain OR speckle tracking), with filters adult (age) and human (subject) applied. To be included, studies needed to report: (I) original data of the mean ± standard deviation or standard error, or median (lower quartile, upper quartile); (II) at least one of left ventricular global longitudinal, circumferential and/or radial strain measured by speckle tracking; (III) in at least 50 healthy individuals; (IV) and either sex must make up at least one third of the healthy cohort. The largest study of healthy subjects were selected when there are multiple studies from the same authors. Healthy subjects are defined by absence of known cardiovascular disease, risk factors including hypertension, diabetes and obesity, chronic disease including malignancy and single or multiorgan failure and cardiac medications, with normal cardiac examination and investigations, both explicitly stated and confirmed by baseline characteristics reported. Reference lists of relevant articles were checked, while case reports, guidelines, editorials and letters were excluded.

Data extraction

We extracted the following parameters from eligible studies into spreadsheets: author surname, year, number of subjects, country, definition of group studied, age, sex, body mass index, systolic blood pressure, heart rate, left ventricular ejection fraction (LVEF), left ventricular end diastolic volume (LVEDV), vendor software, frame rate, and type of strain (2D- or 3D-, and views from which longitudinal strain is measured). The strain outcomes of interest extracted were left ventricular global longitudinal (LVGLS), circumferential (LVGCS) and radial (LVGRS) strains. If strain for endo, mid and epicardial were presented separately, mid-wall strain was recorded. One author (TKMW) screened studies for inclusion and extracted the data, and another author (ZP) confirmed all the appropriate studies for inclusion and data entered.

Statistical analyses

LVGLS, LVGCS and LVGRS by 2D and 3D were separately analyzed. By convention from contemporary echocardiography guidelines and studies, the LLN of strain derived from individual studies of healthy subjects is the boundary of the 95% CI with the lower magnitude of strain, which would be the less negative boundary for LVGLS and LVGCS, and the less positive boundary for LVGRS (7). The process of obtaining pooled mean, pooled lower limit of normal, and corresponding 95% CIs from individual studies using meta-analysis is illustrated in *Figure 1*. The first step is obtaining mean and standard deviation of individual samples (i.e., studies). If medians (med), lower



Figure 1 Schematic illustration of the pooling of mean and lower limit of normal with their respective confidence intervals defined by standard deviation and standard error for any physiological parameter by meta-analysis. LLN, lower limit of normal.

(q1) and upper (q3) quartiles were reported for a study, we used the equations proposed by Wan *et al.* below to derive estimates of the sample mean and standard deviation (11):

Mean = (q1 + med + q3)/3 [1]

 $SD = (q_3 - q_1) / [2 \times \Phi^{-1} (0.75 - 0.125) / (n + 0.25)]$ [2] The mean and SD of mean of individual studies can then be used in meta-analysis to obtain pooled mean and corresponding 95% CI. In an identical manner, we used LLN and SDLLN of individual samples (studies), to calculate the pooled LLN and corresponding 95% CI using meta-analysis. We defined LLN for longitudinal and circumferential strains as the upper boundary of the 95% CI for the sample mean strain calculated as mean plus 1.96 × standard error of the mean as this corresponds to a lower "absolute" (i.e., less negative) value for strain. LLN for radial strain were calculated in a standard manner. To calculate standard error of the lower limit of normal LLN (SE_{LLN}) of individual samples, we used the following formula (where SD_{mean} is the standard deviation of the sample mean and n is number of patients in the sample) (12):

$$SE_{LLN} = \sqrt{SD_{mean}^2} \times \left[\frac{1}{n+2} / (n-1) \right]$$
[3]

From this, we calculated as the parameter k as:

 $\mathbf{k} = \mathbf{SE}_{\text{LLN}} \times \sqrt{(n-1)}$ [4]

Where k is used in conjunction with LLN of individual samples in the same way SD_{mean} is used in conjunction with sample means.

To perform meta-analysis, we pooled both the mean \pm SD_{mean} and LLN ± k across studies using the DerSimonian-Laird method and random effects models. We also analyzed the mean and LLN of LVGLS by baseline characteristics subgroups (either categorical or mean quantitative variables) if reported by at least two studies. Heterogeneity of studies were assessed using the Cochrane Q test (P value) and I^2 (inconsistency) statistic. Study bias was not separately assessed as we were determining abnormal strain thresholds in healthy subjects. Univariable metaregression was used to identify associations between baseline characteristics with LVGLS mean and LLN, using the reported means or medians for continuous variables or proportion for categorical variables for characteristics at study level. A positive beta coefficient indicates higher quantitative parameter or the presence of a categorical



Figure 2 Literature search and disposition of studies.

parameter correlates with a more positive (i.e., less negative or less absolute) strain. The reference group of countries and vendors/programs for comparison were Europe and GE Echopac as they were the most common subgroup for their classifications. Funnel plots were used to assess for publication bias. OpenMeta-Analyst software was used for all analysis (13), and P<0.05 was deemed to be statistically significant.

Results

A total of 773 studies were obtained from the literature search excluding duplicates, and after reviewing all abstracts, 102 studies passed initial screening for full-text review, and 44 studies were eligible for analysis (14-38), totaling 8,910 subjects (*Figure 2*) (39-57). In one study we were able to obtain unpublished means and standard deviations for LVGLS from the authors (15). Characteristics of the eligible studies are displayed in *Table 1*. Studies were published between 2008–2019, the number of healthy subjects varied from 50–2,008, mean age 28–67 years old, and male sex made up 39–65% (overall 50%). 2D-strain was

reported in 38 studies and 3D-strain in 7.

Table 2 lists the pooled means and LLNs with heterogeneity testing of strain parameters on 2D and 3D. For 2D LV strain measurements, the pooled 2D-LVGLS mean and LLN (95% CI) were -20.1% (-20.7%, -19.6%) and -15.4% (-16.0%, -14.7%) respectively (*Figure 3*). The pooled 2D LVGCS mean and LLN (95% CI) were -21.9% (-23.4%, -20.3%) and -15.3% (-16.9%, -13.8%) respectively (*Figure 4*). The pooled 2D LVGRS mean and LLN (95% CI) were 48.4% (43.8%, 53.0%) and 25.5% (17.8%, 33.1%) respectively (*Figure 5*).

For 3D LV strain measurements, the pooled 3D LVGLS mean and LLN (95% CI) were -18.5% (-20.1%, -16.9%) and -14.5% (-16.8%, -12.3%) respectively (*Table 2*). The pooled 3D LVGCS mean and LLN were -25.0% (-30.8%, -19.3%) and -17.6% (-22.6%, -12.6%) respectively. The pooled 3D LVGRS mean and LLN were 49.4% (40.8%, 58.0%) and 27.9% (16.8%, 38.9%) respectively.

Significant heterogeneity was found in all pooled 2D and 3D LV global strain analyses by Cochrane Q test and I^2 statistic. Funnel plots were symmetrical without revealing significant publication bias for all analyses, and the plots for

Table 1 CE	naracter.	istics of	eligible studies													
Author	Year	z	Countries (>1 center)	Healthy controls of disease studied	Age (years)	Male (%)	BMI (kg/m²)	SBP (mmHg)	HR (min ⁻¹)	LVEF (%)	(mL)	Vendor/ software	Frame rate (Hz)	2D/3D	Strain types	GLS views
Abou	2017	94	Netherlands	Cardiovascular risk factors	54±16	57	25±3.4	I	I	I	I	GE EchoPac	I	2D	_	ЗV
Asch	2019	2,008	15 countries	Healthy only	45 [32–65]	51		120 [110–130]	68 [60–75]	Male [57-68] Female [58-69]	Male [61-165] Female [47-122]	TomTec	I	2D	_	30
Bernard	2017	440	Europe [22]	Healthy only	45±13	43	23.9±3.0	119±13	I	59±5	116±30	TomTec	25±6	3D	LCR	3D
Bogunovic	2018	131	Germany	Healthy only	34±13	51	I	I	I	63±5	89±33	GE EchoPac	I	2D	_	ЗV
Cameli	2018	50	Italy	Mitral regurgitation	56±8	56	24.7±5.1	123±14	I	62±3	93±27	GE EchoPac	60-80	2D	_	2V
Caselli	2015	50	Italy	Olympic athletes	28±6	60	I	117±14	73±14	67±7	I	Phillips QLab	54±6	2D	_	ЗV
Degirmenc	i 2017	50	Turkey	Sarcoid	38±5	48	I	120±10	75±8	68±2	I	GE EchoPac	06-09	2D	_	ЗV
Fine	2012	186	NSA	Healthy only	44±16	39	25±5	112±16	72±12	63±4	I	IVV	40–90	2D	LCR	ЗV
Ikonomidis	2015	160	Greece	Hypertension	49±14	50	28.6±4.5	120±10	71±11	71±12	101±23	GE EchoPac	60-80	2D	LCR	3V
Imbalzano	2011	51	Italy	Hypertension	52±13	65	I	122±7	70±13	63±6	86±22	GE EchoPac	60-80	2D	LCR	2V
Inoue	2011	50	Japan	Referred for pacemaker	73±10	58	I	132±14	63±8	69±5	59±15	GE EchoPac	72-102	2D		3V
Jorgensen	2016	234	Denmark	Diabetes	65 (57-70)	65	25.2 (23.1–27.8)	134±17	I	62 (57-65)	I	GE EchoPac	I	2D		3V
Kaku	2014	222	Japan	Referred for MRI	47±16	52	I	126±13	65±10	67±5	I	Phillips TomTec	20.7±5.6	3D	LCR	3D
Kleijn	2015	303	Europe [7], USA	Healthy only	42±14	51	I	I	I	61±3	110±20	Toshiba	I	3D	LCR	3D
Kocabay	2014	247	Italy	Healthy only	44±16	44	23±3	122±14	67±10	63±5	88±22	GE EchoPac	I	2D	LCR	3V
Kotwica	2018	65	Poland	Psoriasis	52.5±10.0	51	25.3±2.9	122±12		69±4	I	GE EchoPac	06-09	2D	_	ЗV
Kusunose	2011	58	Japan	Myocardial infarction	67±11	I	24.2±3.0	133±20	66±10	72±8	I	GE EchoPac	>60	2D		3V
Larsen	2018	67	Denmark	Healthy only	47±15	49	I	122±15	64±10	63±5	I	GE EchoPac	>55	2D	_	ЗV
Lima	2016	58	Brazil	Chaga's disease	37+/12	43	25.4±4.1	122±12	71±11	64±5	109±28	GE EchoPac	40-80	2D	LCR	ЗV
Loncarevic	2016	80	Serbia	Diabetes, hypertension, coronary disease	55±5	54	25.7±3.7	I	I	62±5	I	Esaoate Xstrain	40-90	2D	LC	3V
Table 1 (columnation)	ntinued)															

Table 1 (con	ntinued)															
Author	Year	z	Countries (>1 center)	Healthy controls of disease studied	Age (years)	Male (%)	BMI (kg/m²)	SBP (mmHg)	HR (min ⁻¹)	LVEF (%)	(mL)	Vendor/ software	Frame rate (Hz)	2D/3D	Strain types	GLS views
Maharaj	2012	127	South Africa	Healthy only	39.7±12.1	50	24.9±2.4	124±5	73±10	62.4±7.0	I	Philips QLab	60–80	2D	LCR	1<
Marcus	2011	51	Israel	Healthy only	27±6	59	23.1±2.5	120±12	63±14	75±4	I	GE EchoPac	2000	2D	LCR	1<
Marwick	2009	242	Australia, Germany, USA	Healthy only	51±12	44	I	130 ±16	I	I	I	GE EchoPac	50-70	2D	_	ЗV
Menting	2016	147	Netherlands	Healthy only	44±14	50	24.4±3.3	127±14	I	60±5	119±26	Phillips QLab	>50	2D		3V
Mochizuki	2016	69	Japan	Diabetes	52±16	62	21±3	120±15	65±10	66±5	77±23	GE EchoPac	60–80	2D		3V
Morris	2014	323	Japan, Germany	Hypertension	37±13	57	22.2±12	119 ±10		64±6		GE EchoPac	71±5	2D	LCR	3V
Muraru	2014	265	Italy	Healthy only	45±14	43	23.2±2.9	120±13	72±8	66±10	64±4	GE EchoPac	I	3D	LCR	3D
Ng	2008	122	Australia	Healthy only	44±13	52	25.7±4.9	120±12	I	61±6	I	GE EchoPac	I	2D	ГВ	3V
Reckefuss	2011	144	Germany	Healthy only	42±14	49	24.2±4.2		I	I	I	GE EchoPac	4090	2D	LR	3V
Rodri- guez-Bail- on	2010	105	Spain	Healthy only	49±10	48	24.7±3.3	117±12	I	67±7	I	Siemens WI	60-100	2D	LC	5
Sefa Okten	1 2017	86	Turkey .	Dilated cardiomyopathy 1st degree relatives	32±19	56	I	118±15	I	66±6	I	GE EchoPac	50-90	2D	LCR	30
Shi	2016	119	China	Healthy only	48±9	50	23.5±2.9	110±13	66±10	63±3	45±9	GE EchoPac	74±5	2D	LC	3V
Sugimoto	2017	549	Europe [22]	Healthy only	46±13	41	23.9±3.1	119±13	I	I	I	TomTec	I	2D	LCR	3V
Sullere	2018	707	India	Healthy only	41±11	63	27.2±4.9	123±9	I	61±5	88±21	Phillips QLab	44	2D	_	ЗV
Sun	2013	228	Hong Kong	Healthy only	44±15	48		116±8	I	61±5	81±20	GE EchoPac	06-09	2D	C	ЗV
Tadic	2015	50	Serbia	Diabetes	50±7	48	23.8±2.2	124±13	73±7	64±4	I	GE EchoPac	>30	2D	LCR 2	V+ 3D
														+3D		
Takagiku	2012	817	Japan	Healthy only	36±18	30	I	119±15	67±24	63±7	83±26	GE EchoPac, Phillips QLab, Toshiba	I	2D	LCR	30
Voilliot	2015	53	France	Hypertrophic cardiomyopathy	56±12	45	I	I	64±9	63±4	I	GE EchoPac	>60	3D	LCR	3D
Table 1 (con	ntinued)															

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Table 1 (ω	mtinued)															
Author	Year	z	Countries (>1 center)	Healthy controls of disease studied	Age (years)	Male (%)	BMI (kg/m²)	SBP (mmHg)	HR (min ⁻¹)	LVEF (%)	LVEDV (mL)	Vendor/ software	Frame rate (Hz)	2D/3D	Strain types	GLS views
Wang	2014	50	China	Heart failure	56±5	35	I	I	I	65±4	I	GE EchoPac	I	2D	LCR	3V
Williams	2018	60	Canada, Israel	Hypertrophic cardiomyopathy	32±8	42	I	I	I	67±6	110±20	Siemens WI	I	2D	LC	3V
Xia	2014	153	China	Healthy only	52±16	52	I	I	70±4	58±4		Toshiba	25	3D	LCR	3D
Ν	2018	67	China	Hypertension		65	21.3±2.3	I	67±11	65±6	69+/13	GE EchoPac	I	2D	ГС	2V
Yang	2014	152	Korea	Hypertension	48±8	54	23.0±2.6	115±11	73±11	65±5	I	GE EchoPac	60–80	2D	_	1<
				with exercise												
Yip	2011	60	China	Heart failure	53±10	52	23±3	119±13	70±11	68±4	95±21	GE EchoPac	40-80	2D	LCR	ЗV
Continuot systolic b	is variab ood pre	les are ssure;	e represented b HR, heart rate;	y mean ± standard o LVEF, left ventricula	deviation ir ejection	or med fractio	lian (lower n; 2D, two	quartile-up -dimension	per quar ial; 3D, t	tile) or (95 hree-dime	% confid nsional;	dence interval) VVI, Velocity V	. BMI, bo ector Im	ody mas aging; L	s index; , longitu	SBP, dinal;

C, circumferential; R, radial strains; 3V, 4, 2 and 3 chamber views (3 views); 2V, 4 and 2 chamber views (2 views); 1V, 4-chamber only (1 view). Gaps are missing data not

reported by studies

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2D-LVGLS mean and LLN are shown in (Figure 6).

Results of the meta-regression analysis for 2D-LVGLS are shown in *Table 3*. The only factor associated with 2D-LVGLS means and LLNs was vendor software, specifically velocity vector imaging (VVI) having less negative values than GE Echopac. There was no significant interaction between LVGLS mean or LLN with year of publication, sex, region, body mass index, heart rate, systolic blood pressure, left ventricular ejection fraction or end-diastolic volume, other vendors and frame rate.

Discussion

Prior meta-analyses of LV strain assessment in healthy subjects focused on accurately defining the point estimate of the pooled average LV strain (8,9). A recent updated metaanalysis was able to use patient-level data in 16 studies and 2,396 subjects to determine the pooled means with 95% CIs and LLN of LVGLS only by vendor (10). The novelty of our findings is that we now also provide the estimate for the pooled LLN and the 95% CI of LLN using meta-analysis techniques for LVGLS, LVGCS and LVGRS, and for 2Dand 3D-strain, on top of being able to pool larger number of patients at the study level. This information is highly relevant as it can help define what should be considered an abnormal strain value in clinical practice. We also provide meta-regression results showing persistence of a small, but still present, between-vendor difference in strain despite recommendations for standardization of strain imaging with different LLNs (6). Finally, we did not detect any temporal trends in strain variability for both mean value and lower limit of normal. Notably, we focused on healthy participants with no cardiovascular disease or risk factors that could affect LV strain measurement so some large population studies were excluded (58,59), and also excluded studies that didn't use speckle-tracking to measure LV strain such as tissue Doppler techniques (60).

Interpretation of the pooled means and LLNs for normal strain

The goal of meta-analysis is to combine results from multiple studies that address a similar question in order to increase power of point estimate of some clinically relevant parameter. Most commonly, we seek to obtain pooled parameters of a single important point estimate, such as relative risk or odds ratio. In that manner previous metaanalyses of LV strain in healthy subjects focused on a point

		icu means	and low	ci minto o	normai ioi two and	i three unitensional left ve	intricular gi	obai strain	
Ś	Strain	Studies	Ν	Mean	95% CI (mean)	Heterogeneity testing	LLN	95% CI (LLN)	Heterogeneity testing
2	2D								
	GLS (%)	38	7,430	-20.1%	-20.7%, -19.6%	3,828 (<0.001), 99.0%	-15.4%	-16.0%, -14.7%	173 (<0.001), 97.9%
	GCS (%)	31	2,990	-21.9%	-23.4%, -20.3%	3,530 (<0.001), 99.5%	-15.3%	–16.9%, –13.8%	1,231 (<0.001), 98.5%
	GRS (%)	16	2,597	48.4%	43.8%, 53.0%	2,368 (<0.001), 99.4%	25.5%	17.8%, 33.1%	2,182 (<0.001), 99.3%
3	3D								
	GLS (%)	7	1,486	-18.5%	-20.1%, -16.9%	1,084 (<0.001), 99.4%	-14.5%	–16.8%, –12.3%	723 (<0.001), 99.2%
	GCS (%)	6	1,436	-25.0%	-30.8%, -19.3%	5,770 (<0.001), 99.9%	-17.6%	-22.6%, -12.6%	1,436 (<0.001), 99.7%
	GRS (%)	6	1,436	49.4%	40.8%, 58.0%	1,937 (<0.001), 99.7%	27.9%	16.8%, 38.9%	162 (<0.001), 96.9%

Table 2 Pooled means and lower limits of normal for two- and three-dimensional left ventricular global strain

Heterogeneity testing includes the Cochrane Q (P value) and I². 95% CI, 95% confidence interval; LLN, lower limit of normal; 2D, two-dimensional; GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; 3D, three-dimensional.

estimate of pooled mean strain, with a corresponding 95% CI providing a measure of precision of this point estimate (8,9). However, as pooled 95% CI of the mean depend on sample size, they eventually become narrow with larger numbers, and do not reflect the general distribution of strain values in healthy subjects. These issues prompted us to develop a meta-analysis approach to define the LLN, with the specific purpose of detecting threshold beyond which strain measurements become "abnormal". We addressed this task by emulating the approach of Bland who reported an elegant formula for estimating the standard error for the boundaries of the 95% CI of the mean, i.e., LLN (12). We can then combine these LLNs in a metaanalysis fashion to estimate the pooled LLN and its 95% CI for all strain parameters. With this approach it is important to note that, by default, the pooled standard error for the LLN is higher than that of the pooled standard error of the mean. Furthermore, if we used 99% confidence interval for our definition of the LLNs, the estimated LLN would be even further from the mean with its own, wider, confidence interval.

How should the pooled LLNs found in this metaanalysis be interpreted? Using the LLN of 2D-LVGLS as an example, the pooled estimate of -15.4% could be set as the cut-point for abnormal 2D-LVGLS. However, the 95% CI of LLN, in this case -16.0% to -14.7% presents further complexities to its interpretation, as this is the range for which the real LLN is thought to most likely (but not definitely) lie. The pragmatic approach to its use this would be if 2D-LVGLS was below (more negative than) -16.0%then it is normal, and if it is above (less negative) than -14.7%, then it is abnormal. The range of values between -16.0% to -14.7% would then be in the borderline grey zone. Our pooled LLN for LVGLS is similar to the -18% to -14% LLNs depending on vendor in the most recent updated meta-analysis (10).

The pooled means do have value in illustrating the average strain values for healthy subjects, subgroups and allow comparisons between studies. Our updated metaanalysis reported similar pooled means (95% CI) to the -19.7% (-20.4%, -18.9%), -23.3% (-24.6%, -22.1%) and 47.3% (43.6%, 51.0%) for 2D-LVGLS, LVGCS and LVGRS respectively reported in the earliest 2D-LV strain meta-analysis (8), and the more recent updated metaanalysis -21.0% (-19.2%, -22.7%) (10). We also found similar pooled means for 3D-LV strain to the -19.1% (-19.9%, -18.2%), -22.4% (-21.0%, -23.9%) and 47.5% (41.5-53.5%) reported in the previous 3D-LV strain metaanalysis (9), and in fact, 3D and 2D estimates were also similar. Still, there remains a significant heterogeneity between individual studies observed in previous metaanalyses and ours, even though the pooled mean LV strains for healthy subjects were consistent, reflecting the multitude of factors that influence these measurements (8,9).

Factors that influence strain by subgroups and regression

The only parameter we found on meta-regression for both the mean and LLN of 2D-LVGLS was vendor software. VVI had less negative 2D-LVGLS mean (by 2.8%) and LLN (by 3.9%) than GE Echopac whereas the Phillips QLab and Tomtech did not. The earliest 2D-LVGLS metaanalysis compared non-GE versus GE vendor software in its meta-regression, and this was not associated with mean 2D-LVGLS, although P value was 0.08 and VVI was not specifically analyzed (8). The more recent updated meta-

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Figure 4 Left ventricular global circumferential strain pooled (A) mean and (B) lower limit of normal.

analysis reported separate pooled means and LLNs by vendor software (GE –21.2% and –18.2%, Toshiba –19.9% and –15.8%, Philips –19.6% and –15.5%, and Siemens –16.9% and –14.0% respectively) showed similar pattern to our findings (10). Furthermore, vendor software was significantly associated with 3D-strain in the other previous meta-analysis, where Toshiba and 3DWM tracking software

had less negative mean 3D-LVGLS than Echopac, GE and Phillips (9). Other studies including a wider distribution of normal and abnormal strains have also found VVI to produce less negative values to GE (61). We therefore recommend using a different LLN for VVI adjusted by the meta-regression beta-coefficient from the overall values, or using one of the alternative vendor software instead.



Figure 5 Left ventricular global radial strain pooled (A) mean and (B) lower limit of normal.

Further large studies are required to establish this threshold for VVI as current data (two studies in this meta-analysis) is limited.

Limitations

This meta-analysis has some limitations. We assumed that all eligible studies had experienced readers following standardized methods and accurately measured LV strain which may not always be the case (6). Smaller studies and those with over-representation of male or female populations by more than two thirds were excluded to reduce bias, although this reduced the total number of subjects that couldn't have been meta-analyzed with higher power. Heterogeneity was present for the range of normal LV strain reported across studies, as well as study design, populations and equipment, however this is expected and presented in all previous strain meta-analyses (8,9), and we also analyzed for parameters that may affect variations in LV strain measurements. Subgroup analysis particularly for the minority groups like the elderly age-group and non-GE vendors have wider 95% CI and may be underpowered. Notably, we defined LLN mathematically as the boundary of the 95% CI of the mean from individual studies and

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Figure 6 Funnel plots to assess for publication bias for the pooled (A) means and (B) LLN of 2D-LVGLS. LLN, lower limit of normal; LVGLS, left ventricular global longitudinal strain.

Table 3 Meta-regression of left ventricular global longitudinal strain mean and lower limit of normal

Deremeter		LVGLS mean			LVGLS LLN	
Farameter	Beta	95% CI	P value	Beta	95% CI	P value
Year study published	0.00	-0.19, 0.18	0.968	-0.21	-0.45, 0.03	0.082
Age (years)	0.02	-0.03, 0.08	0.432	0.04	-0.03, 0.11	0.273
Male (%)	0.01	-0.07, 0.08	0.846	-0.02	-0.12, 0.08	0.665
Asian (versus European)	-0.96	-2.09, 0.18	0.097	-0.64	-2.29, 1.01	0.446
Body mass index (kg/m²)	0.24	-0.11, 0.60	0.175	0.33	-0.11, 0.76	0.140
Systolic blood pressure (mmHg)	0.07	-0.03, 0.18	0.169	0.11	-0.04, 0.27	0.159
Heart rate (/minute)	0.04	-0.13, 0.20	0.642	0.00	-0.23, 0.22	0.977
Left ventricular ejection fraction (%)	-0.07	-0.24, 0.11	0.445	-0.11	-0.32, 0.10	0.288
Left ventricular end-diastolic volume (mL)	0.01	-0.03, 0.06	0.584	-0.01	-0.06, 0.04	0.611
Vendor software						
Phillips QLab (versus GE Echopac)	1.03	-0.49, 2.54	0.184	1.10	-0.97, 3.18	0.297
Tomtec (versus GE Echopac)	-1.48	-3.53, 0.57	0.157	-1.48	-4.27, 1.31	0.298
VVI (versus GE Echopac)	2.76	1.03, 4.50	0.002	3.92	1.53, 6.31	0.001
Non-GE (versus GE Echopac)	1.72	-1.16, 4.59	0.241	0.62	-3.31, 4.55	0.757
Frame rate (/s)	0.04	-0.03, 0.11	0.238	0.04	-0.08, 0.16	0.517

Italic numbers refer to those with P values <0.05. LVGLS, left ventricular global longitudinal strain; LLN, lower limit of normal; VVI, Velocity Vector Imaging.

pooled this, which is by convention and arbitrary for echocardiographic chamber quantification (7) but also not based on prognostic significance. The meta-regression analysis has some biases and power in terms of missing baseline characteristics in some studies as well as the lack of patient-level data. Publication bias may be present as for any meta-analysis although we did not find significant evidence for this.

Conclusions

This meta-analysis study aimed to define the thresholds

of abnormal LV strains in healthy subjects by determining the pooled LLN and the 95% confidence interval of LLN. Based on this, we can classify LV strain parameters as normal, borderline or abnormal. For example, for 2D-LVGLS the pooled LLN (95% CI) was -15.4% (-16.0%, -14.7%), therefore if 2D-LVGLS is less negative than -14.7% it would be abnormal, between -16.0% and -14.7% would be borderline, and more negative than -16.0% is normal. The pooled LLNs and updated pooled mean for 2D and 3D LVGLS, LVGCS and LVGRS parameters are provided. Meta-regression analysis revealed significant differences in LV strain by vendor software, but no differences by time, clinical or echocardiographic factors. These abnormal and borderline thresholds and methodology and methodology have significant clinical and academic applications for future practice and studies of LV strain.

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Footnote

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