Defining the Reference Range for Left Ventricular Strain in Healthy Patients by Cardiac MRI Measurement Techniques: Systematic Review and Meta-Analysis

Tom Kai Ming Wang, MD, PhD[1,2], Deborah H. Kwon, MD[1,2], Brian P. Griffin, MD[1], Scott D. Flamm, MD[1,2], Zoran B. Popović, MD, PhD[1,2]

Evidence Synthesis and Decision Analysis · Systematic Review/Meta-Analysis

Keywords

heart, feature tracking, meta-analysis, MRI, strain, tagging

Submitted: Jun 30, 2020
Revision requested: Jul 21, 2020
Revision received: Aug 12, 2020
Accepted: Oct 15, 2020
First published online: Oct 21, 2020

The authors declare that they have no disclosures relevant to the subject matter of this article.

Supported by the National Heart Foundation of New Zealand Overseas Clinical and Research Fellowship (grant no. 1775) to T. K. M. Wang. The funder was not specifically involved in the design or conduct of this study.

An electronic supplement is available online at doi.org/10.2214/AJR.20.24264.

BACKGROUND. Echocardiography is the primary noninvasive technique for left ventricular (LV) strain measurement. MRI has potential advantages, although reference ranges and thresholds to differentiate normal from abnormal left ventricular global longitudinal strain (LVGLS), left ventricular global circumferential strain (LVGCS), and left ventricular global radial strain (LVGRS) are not yet established.

OBJECTIVE. The purpose of our study was to determine the mean and lower limit of normal (LLN) of MRI-derived LV strain measurements in healthy patients and explore factors potentially influencing these measurements.

EVIDENCE ACQUISITION. PubMed, Embase, and Cochrane Library databases were searched for studies published through January 1, 2020, that reported MRI-derived LV strain measurements in at least 30 healthy individuals. Mean and LLN measurements of LV strain were pooled using random-effects models overall and for studies stratified by measurement method (feature tracking [FT] or tagging). Additional subgroup and meta-regression analyses were performed.

EVIDENCE SYNTHESIS. Twenty-three studies with a total of 1782 healthy subjects were included. Pooled means and LLNs for all studies were –18.6% (95% CI, –19.5% to –17.6%) and –13.3% (–13.9% to 12.7%) for LVGLS, –21.0% (–22.4% to –19.6%) and –15.6% (–17.0% to –14.3%) for LVGCS, and 38.7% (30.5–46.9%) and 20.6% (15.1–26.1%) for LVGRS. Pooled means and LLNs for LVGLS by strain measurement method were –19.4% (95% CI, –20.6% to –18.1%) and –13.1% (–14.2% to –12.0%) for FT and –15.6% (–16.2% to –15.1%) and –13.1% (–14.1% to –12.2%) for tagging. A later year of study publication, increasing patient age, and increasing body mass index were associated with more negative mean LVGLS values. An increasing LV end-diastolic volume index was associated with less negative mean LVGLS values. No factor was associated with LLN of LVGLS.

CONCLUSION. We determined the pooled means and LLNs, with associated 95% CIs, for LV strain by cardiac MRI to define thresholds for normal, abnormal, and borderline strain in healthy patients. The method of strain measurement by MRI affected the mean LVGLS. No factor affected the LLN of LVGLS.

CLINICAL IMPACT. This meta-analysis lays a foundation for clinical adoption of MRI-derived LV strain measurements, with management implications in both healthy patients and patients with various disease states.

Introduction

Left ventricular global longitudinal strain (LVGLS), left ventricular global circumferential strain (LVGCS), and left ventricular global radial strain (LVGRS) measurements are established parameters for assessing left ventricular (LV) systolic function and have prognostic utility across a range of cardiovascular diseases [1–3]. Echocardiography is the primary noninvasive technique used for these measurements because of its widespread availability, accessibility, and perceived low cost [2]. MRI offers superior spatial and contrast resolution compared with echocardiography [4]. However, its adoption was hindered by the need for a dedicated pulse sequence when using the initial method for MRI strain measurement (myocardial tagging, introduced in 1988) and a lag in the development of MRI

doi.org/10.2214/AJR.20.24264
AJR 2021; 217:569–583
ISSN-L 0361–803X/21/2173–569

[1]Department of Cardiovascular Medicine, Section of Cardiovascular Imaging, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195. Address correspondence to Z. B. Popović (popoviz@ccf.org).

[2]Section of Cardiovascular Imaging, Imaging Institute, Cleveland Clinic, Cleveland, OH.

postprocessing software that offers high precision and reproducibility. Feature tracking (FT), introduced in 1994, does not need a dedicated sequence and became more widely used than myocardial tagging for strain measurement with MRI; further methods introduced for MRI strain measurement were displacement encoding with stimulated echoes (DENSE) in 1999 and strain-encoding (SENC) imaging in 2009 [5]. Despite these advances, echocardiography has remained the mainstay noninvasive technique for this purpose.

Prior meta-analyses addressed strain measurements in healthy patients, including LV (2D and 3D), right ventricular (RV), and left atrial strains by echocardiography as well as LV and RV strains by MRI [6–10]. These meta-analyses serve to combine reported experiences across the literature to increase the power for reporting the estimates of parameters such as means, proportions, odds ratios, and c-statistics. Establishing the lower limit of normal (LLN) for LV strain for healthy patients is important clinically to influence surveillance and treatment decisions. However, prior meta-analyses pooled the mean strain of healthy patients at the study level and used the 95% CI of that estimate as the normal reference range. This method produces a precise estimate of the mean with a very narrow 95% CI; however, the 95% CI no longer reflects the distribution of normal strain values in the healthy population. Therefore, the boundaries of this 95% CI of the pooled mean should not be used as the threshold to define normal and abnormal strain values. Furthermore, the clinical and MRI factors that affect MRI-derived LV strain values have not been previously investigated.

This meta-analysis aimed to separately pool the means and LLNs of LV strain measured by MRI from studies of healthy patients and to determine whether patient and MRI factors influence LV strain

HIGHLIGHTS

Key Finding

- *For left ventricular (LV) strain MRI measurements, lower limits of normal (LLNs) and 95% CIs were less affected than mean values by patient and MRI factors. LLN for LV global longitudinal strain was –13.3% (95% CI, –13.9% to 12.7%) overall, –13.1% (–14.2% to –12.0%) with feature tracking, and –13.1% (–14.1% to –12.0%) with tagging.*

Importance

- *Thresholds of abnormal, borderline, and normal LV strains by MRI can be defined on the basis of pooled LLNs and 95% CIs for healthy patients.*

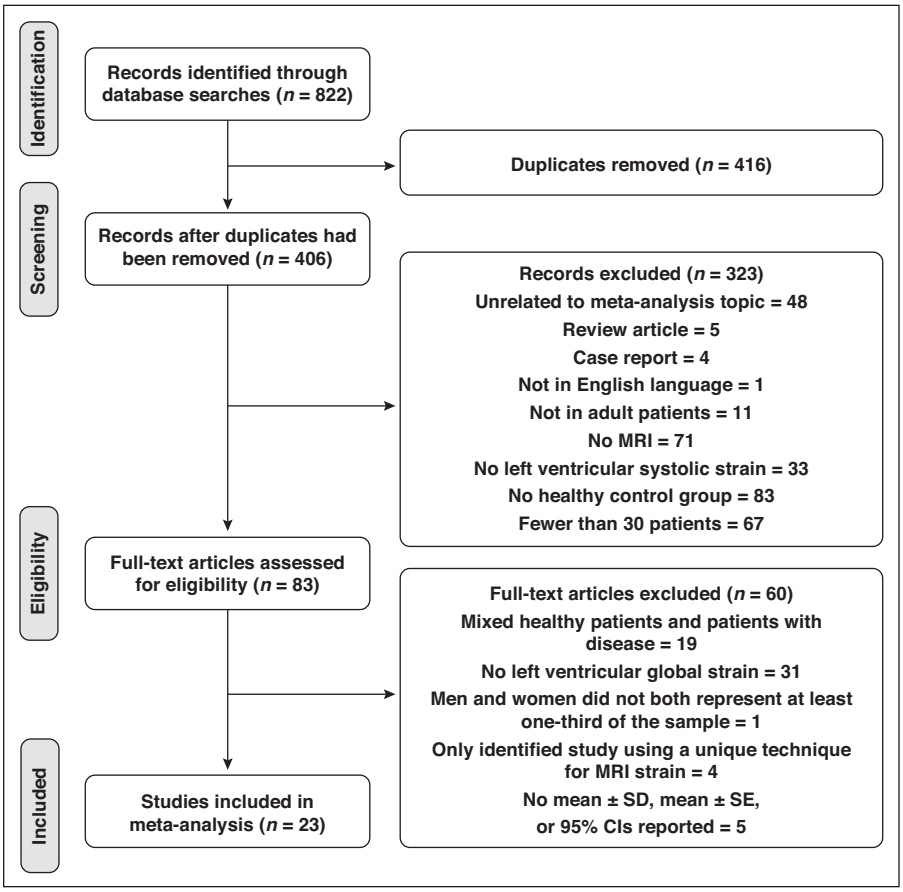


Fig. 1—PRISMA flow diagram shows selection of eligible studies from literature search. SE = standard error.

values. By pooling the LLNs of strain, the reference ranges for normal, abnormal, and borderline strains can be defined.

Evidence Acquisition

Literature Search and Inclusion Criteria

This meta-analysis was performed in accordance with PRISMA guidelines. We searched PubMed, Cochrane Library, and Embase databases on January 1, 2020, for eligible studies published through that date using the following search terms: (left ventricle) AND (MRI) AND (strain). Search results were restricted to studies of both humans and adults. Entire articles were searched for the search terms when this option was available. Only original research studies were reviewed; review articles, editorials, guidelines, and case reports and articles written in a language other than English were excluded. Eligible studies needed to report measurements estimating the mean and spread (SD, standard error [SE], or 95%

TABLE 1: Characteristics of Study Design and MRI Technique of Eligible Studies

First Author [Reference No.]	Year[a]	No. of Patients	Patients or Disease Studied	Country	Vendor	Field Strength (T)	Method	Software	Strain	Long Axis	Short Axis
Andre [12]	2015	150	Healthy subjects	Germany	Philips	1.5	FT	2DCPA[b]	L, C, R	MP	ML
Augustine [13]	2013	145	Healthy subjects	UK	Siemens	1.5	FT and tagging	2DCPA[b] and CIMTag2D[c]	L, C, R	MP	ML
Cao [14]	2018	32	DM	China	Siemens	1.5	FT	cvi42[d]	L, C, R	MP	ML
Doerner [15]	2018	30	Myocarditis	Germany	Philips	1.5	FT	2DCPA[b]	L, C	4-Ch	Mid
Edwards [16]	2015	43	CKD	UK	Siemens	1.5	FT	Diogenes[b]	L	4-Ch	NR
Holloway [17]	2013	39	HIV	UK	Siemens	3	Tagging	CIMTag2D[c]	L, C	4-Ch	Mid
Homsi [18]	2019	41	Obesity	Germany	Philips	1.5	FT	2DCPA[b]	L, C	MP	Mid
Lawton [19]	2011	60	Healthy subjects	USA	Siemens	1.5	Tagging	StressCheck[e]	L, C, R	NR	ML
Lewandowski [20]	2013	132	Adults born preterm	UK	Siemens	1.5	FT	2DCPA[b]	L	4-Ch	NR
Li [21]	2017	35	AL-amyloidosis	China	Siemens	3	FT	cvi42[d]	L, C, R	MP	ML
H. Liu [22]	2017	130	Healthy subjects	China	Siemens	3	FT	TrufiStrain[f]	L, C, R	4-Ch	ML
X. Liu [23]	2017	30	Ebstein anomaly	China	Siemens	3	FT	cvi42[d]	L, C, R	MP	ML
B. Liu [24]	2018	100	Healthy subjects	UK	Siemens	1.5	FT	cvi42[d]	L, C, R	4-Ch	Mid
Maniar [25]	2004	32	CABG	USA	Siemens	1.5	Tagging	StressCheck[e]	C	NR	Mid
Moody [26]	2015	35	DCM	UK	Siemens	1.5	FT and tagging	Diogenes[b] and CIMTag2D[c]	L, C	4-Ch	Mid
Peng [27]	2018	150	Healthy subjects	China	Siemens	1.5 or 3	FT	Medis Suite[g]	L, C, R	MP	ML
Riffel [28]	2015	234	CM	Germany	Philips	1.5	FT	2DCPA[b]	L	MP	NR
Rodríguez-Bailón [29]	2010	32	HTN	UK	Siemens	1.5	FT	cvi42[d]	R	NR	NR
Shang [30]	2019	36	DM	China	Siemens	3	FT	cvi42[d]	L, C, R	4-Ch	Mid
Swoboda [31]	2016	35	Athletes	UK	Philips	3	Tagging	inTag[h]	L	4-Ch	NR
Taylor [32]	2015	100	Healthy subjects	UK	Siemens	1.5	FT	Diogenes[b]	L, C, R	MP	ML
Venkatesh [33]	2015	129	High CV risk	USA	Siemens and GE	1.5	Tagging	HARP[i]	C, R	NR	ML
Xu [34]	2017	32	HCM	China	Siemens	3	FT	cvi42[d]	L, C, R	MP	ML

Note—Philips = Philips Healthcare, FT = feature tracking, 2DCPA = 2D cardiac performance analysis, L = longitudinal, C = circumferential, R = radial, MP = multiplanar, ML = multilevel, Siemens = Siemens Healthcare, DM = diabetes mellitus, 4-Ch = four-chamber, CKD = chronic kidney disease, NR = not reported, AL = amyloid light-chain, CABG = coronary artery bypass grafting, DCM = dilated cardiomyopathy, CM = cardiomyopathy, HTN = hypertension, CV = cardiovascular, GE = GE Healthcare, HARP = Harmonic Phase, HCM = hypertrophic cardiomyopathy.

[a]Year of publication.
[b]TomTec Imaging Systems.
[c]University of Auckland.
[d]Circle Cardiovascular Imaging.
[e]ESRD.
[f]Siemens Healthcare.
[g]Version 3.0, Medis Medical Imaging.
[h]Version 1.0, Creatis.
[i]Diagnosoft.

CI) of values for at least one type of LV global strain (LVGLS, LVGCS, or LVGRS) in healthy individuals. In addition, both men and women needed to constitute at least one-third of the study sample. To be eligible for the primary systematic review and meta-analysis, studies further needed to include at least 30 healthy individuals. Studies of new methods of strain measurements that were not reported by at least two studies with at least 30 patients were included in separate analyses of those methods if at least two studies with at least 10 patients were identified for a given method. Some studies defined healthy individuals as the absence of cardiovascular and other chronic diseases including malignancy and organ failure, absence of cardiovascular risk factors including hypertension and diabetes, and absence of cardiac medications. If the study did not explicitly define healthy individuals, then the baseline characteristics of the study sample were reviewed to ensure eligibility.

Data Collection

The lead investigator (T.K.M.W., a cardiologist with 2 years of experience) initially screened the abstracts of all studies identified from the literature search. The full texts of potentially eligible articles were then adjudicated for inclusion in the final analysis by three investigators (T.K.M.W.; D.H.K., a cardiologist with 10 years of experience; and Z.B.P., a cardiologist with 22 years of experience). The lead investigator (T.K.M.W.) extracted data from the included studies for the subsequent meta-analysis.

Study characteristics extracted included the first author's last name, year of publication, number of patients, disease studied (if applicable), and country in which the study was performed. MRI hardware and software characteristics extracted included machine vendor, magnetic field strength in Tesla, strain measurement method (FT, tagging, DENSE, or SENC), analysis software, axis of strain measured (LVGLS, LVGCS, or LVGRS), and planes of strain measured on long- and short-axis images. Clinical characteristics extracted included age, sex, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume index (LVEDVI), and left ventricular mass index (LVMI).

TABLE 2: Characteristics of Subjects of Eligible Studies

First Author [Reference No.]	No. of Patients	Age (y)	Sex (%)		BMI	SBP (mm Hg)	DBP (mm Hg)	HR (bpm)	LVEF (%)	LVEDVI (mL/m^2)	LVMI (g/m^2)
			M	F							
Andre [12]	150	46 ± 14	50	50	24 ± 3	126 ± 11	76 ± 9	NR	NR	NR	NR
Augustine [13]	145	30 ± 8	37	63	24 ± 4	116 ± 12	71 ± 8	67 ± 9	64 ± 5	NR	55 ± 10
Cao [14]	32	54 ± 6	53	47	24 ± 2	124 ± 10	758	66 ± 9	57 ± 5	64 ± 11	56 ± 7
Doerner [15]	30	37 ± 13	47	53	23 ± 3	NR	NR	60 ± 11	62 ± 5	80 ± 14	NR
Edwards [16]	43	57 ± 10	56	44	26 ± 5	126 ± 11	77 ± 8	NR	73 ± 6	62 ± 10	58 ± 10
Holloway [17]	39	40 (37–52)[a]	67	33	24 (23–26)[a]	131 (122–143)[a]	78 (70–86)[a]	NR	70 (66–74)[a]	76 (70–88)[a]	NR
Homsi [18]	41	57 ± 16	46	54	25 ± 2	125 ± 11	79 ± 7	67 ± 12	66 ± 4	69 ± 15	54 ± 7
Lawton [19]	60	33 ± 11	47	53	NR	120 ± 13	74 ± 10	NR	NR	NR	NR
Lewandowski [20]	132	27 ± 5	46	54	24 ± 6	NR	NR	NR	64 ± 5	81 ± 12	NR
Li [21]	35	51 ± 9	49	51	NR	NR	NR	NR	62 ± 7	NR	NR
H. Liu [22]	130	47 ± 17	46	54	23 ± 3	119 ± 10	78 ± 9	73 ± 9	66 ± 6	73 ± 12	49 ± 8
X. Liu [23]	30	34 ± 13	53	47	21 ± 2	NR	NR	NR	65 ± 4	125 ± 27	NR
B. Liu [24]	100	45 ± 14	50	50	26	NR	NR	NR	71 ± 7	65 ± 12	57 ± 12
Maniar [25]	32	30 ± 8	53	47	NR	NR	NR	NR	NR	NR	NR
Moody [26]	35	40 ± 12	62	38	NR	120 ± 11	72 ± 6	66 ± 10	71 ± 6	NR	64 ± 11
Peng [27]	150	51 ± 15	50	50	24 ± 3	NR	NR	72 ± 14	65 ± 7	67 ± 11	44 ± 9
Riffel [28]	234	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rodríguez-Bailón [29]	32	49 ± 11	56	44	26 ± 5	126 ± 12	77 ± 10	NR	64 ± 7	77 ± 18	58 ± 11
Shang [30]	36	51 ± 12	47	53	24 ± 3	117 ± 9	80 ± 7	NR	58 ± 5	64 ± 10	49 ± 8
Swoboda [31]	35	31 ± 9	67	33	25 ± 3	115 ± 11	59 ± 11	65 ± 9	58 ± 4	NR	52 ± 9
Taylor [32]	100	45 ± 14	50	50	26	123 ± 12	73 ± 7	67 ± 11	72 ± 6	63 ± 10	59 ± 12
Venkatesh [33]	129	59 ± 9	35	65	24 ± 3	113 ± 12	67 ± 9	NR	69 ± 6	NR	68 ± 10
Xu [34]	32	45 ± 16	56	44	NR	NR	NR	80 ± 13	63 ± 6	NR	NR

Note—Unless otherwise indicated, values are mean ± SD. BMI = body mass index (weight in kilograms divided by the square of height in meters), SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, LVEF = left ventricular ejection fraction, LVEDVI = left ventricular end-diastolic volume index, LVMI = left ventricular mass index, NR = not reported.

[a]Median (lower quartile–upper quartile).

Risk of Bias

Factors that potentially introduce bias in this analysis were considered. Risks of bias were evaluated for all eligible studies in the categories of patient selection, index test, and flow and timing. No reference standard was used. The patient selection category assessed the definition of healthy individuals, inclusion of a disease group, and demographic factors. The index test category assessed whether the strain measurement was fully automated or semiautomated (i.e., involved manual tracing). The flow and timing category assessed if the study was prospective or retrospective and whether MRI was performed at baseline.

Statistical Analyses

LVGLS, LVGCS, and LVGRS means and LLNs were pooled across all studies and by the method of strain measurement if reported by two or more studies. If a study reported more than one set of mean and spread of strain by different methods of strain measurement in the same sample of healthy individuals, then all these measurement sets were all used for pooling of all studies and were separately used in subgroup analyses. Both the mean and LLN of strain with their SEs were pooled to calculate the pooled mean and LLN with 95% CIs. LLN was defined as the upper (less negative) boundary of the 95% CI for the sample mean strain for LVGLS and LVGCS and as the lower (less positive) boundary of the 95% CI for the sample mean strain for LVGRS. The SE of LLN (SE_{LLN}) was calculated using the formula previously proposed by Bland [11]:

$$SE_{LLN} = \sqrt{(SD_{mean}{}^2 \times (1 / n + 2 / (n - 1)))},$$

where SD_{mean} is the sample mean's SD, and n is the number of patients in the sample.

We also calculated the following:

$$SE_{LLN} \times \sqrt{(n - 1)}.$$

This parameter can be used with LLN in the same way that the mean and the SD of the mean are used for meta-analysis.

The DerSimonian-Laird method using random-effects models was used for pooled analysis. The analysis was performed for all eligible studies, and the results were then stratified by the method of strain measurement given that the measurement method was anticipated to be an important factor determining the strain value. Separate pooled analyses were performed for new methods of strain measurements that were reported in at least two studies with at least 10 patients but not for new methods of strain measurements that were reported in at least two studies with at least 30 patients. The Cochrane Q test (p value) and I^2 (inconsistency) statistic were used to assess heterogeneity.

Subgroup analysis of pooled LVGLS mean and LLN were performed by the method of strain measurement, software, machine vendor, magnetic field strength, and long-axis views if reported by at least two studies. Associations between clinical and MRI characteristics with LVGLS mean and LLN in all studies and by the method of strain measurement were evaluated using univariable meta-regression and reporting beta coefficients, the 95% CIs of the beta coefficients, and p values.

For categoric subgroups, comparisons were performed for countries in Asia versus the United States, Australia, and countries in Europe; tagging versus FT; MRI scanner vendor of Philips Healthcare versus Siemens Healthcare; 3-T versus 1.5-T field strength; and long-axis four-chamber views only versus multiplanar views for LVGLS. Publication bias was assessed using fun-

TABLE 3: Pooled Estimates of LV Strain of All Eligible Studies and Studies by Measurement Method

LV Strain	No. of Studies	No. of Patients	Mean (%)	95% CI (%)	Heterogeneity Testing			LLN (%)	95% CI (%)	Heterogeneity Testing		
					Cochrane *Q*	*p*	I^2 (%)			Cochrane *Q*	*p*	I^2 (%)
All eligible studies												
LVGLS	22	1769	–18.6	–19.5 to –17.6	3813	< .001	99.5	–13.3	–13.9 to 12.7	454	< .001	95.4
LVGCS	20	1341	–21.0	–22.4 to –19.6	3356	< .001	99.4	–15.6	–17.0 to –14.3	926	< .001	98.1
LVGRS	15	1306	38.7	30.5–46.9	13,912	< .001	99.9	20.6	15.1–26.1	2003	< .001	99.3
FT studies											< .001	
LVGLS	17	1455	–19.4	–20.6 to –18.1	1448	< .001	98.9	–13.1	–14.2 to –12.0	321	< .001	95.0
LVGCS	14	901	–21.9	–24.3 to –19.5	3196	< .001	99.6	–15.8	–18.1 to –13.6	754	< .001	98.4
LVGRS	12	972	44.3	38.1–50.5	1717	< .001	99.4	24.0	17.4–30.6	630	< .001	98.3
Tagging studies												
LVGLS	5	314	–15.6	–16.2 to –15.1	123	< .001	96.8	–13.1	–14.1 to –12.2	130	< .001	96.9
LVGCS	6	440	–19.0	–19.5 to –18.5	45	< .001	88.9	–15.1	–16.8 to –13.5	171	< .001	97.1
LVGRS	3	334	16.2	11.2–21.2	404	< .001	99.5	7.8	3.5–12.1	99	< .001	98.0

Note—LV = left ventricular, LLN = lower limit of normal, LVGLS = left ventricular global longitudinal strain, LVGCS = left ventricular global circumferential strain, LVGRS = left ventricular global radial strain, FT = feature tracking.

nel plots and the Egger statistic. All analyses were performed using OpenMeta-Analyst software [12]. Statistical significance level was set at .05.

Evidence Synthesis

Literature Search and Eligible Studies

The literature search yielded 406 unique studies. After the abstracts of all the studies had been screened, there were 83 potentially eligible studies. The full-text versions of these 83 studies were evaluated. Twenty-three studies totaling 1782 healthy patients were included for the meta-analysis [12–34] (Fig. 1). The study design and MRI characteristics for the eligible studies are shown in Table 1, and the patient characteristics for the eligible studies are shown in Table 2. The studies were published between 2004 and 2019, and the number of healthy patients in each study ranged from 30 to 234. Mean age ranged from 27 to 59 years. The percentages of male patients and female patients ranged from 37% to 67%.

Risk of Bias

Table S1, which can be viewed in the *AJR* electronic supplement to this article at www.ajronline.org, provides details pertaining to the risk-of-bias evaluation in the 23 included studies. In terms of patient selection, nine studies did not define the criteria for healthy individuals, and seven studies evaluated only healthy individuals without a disease group. In terms of the index test, only one study used fully automated software, whereas the remaining studies used manual tracing with semiautomated strain software. In terms of flow and timing, two studies were retrospective with unknown timing of the MRI examination relative to patient inclusion, and the remaining studies were prospective with MRI examinations performed at baseline. A total of 12 studies both had defined criteria for healthy individuals and used a prospective study design.

Overall Pooled Analyses

The pooled means and LLNs for all eligible studies, studies of FT, and studies of tagging for LVGLS, LVGCS, and LVGRS are displayed

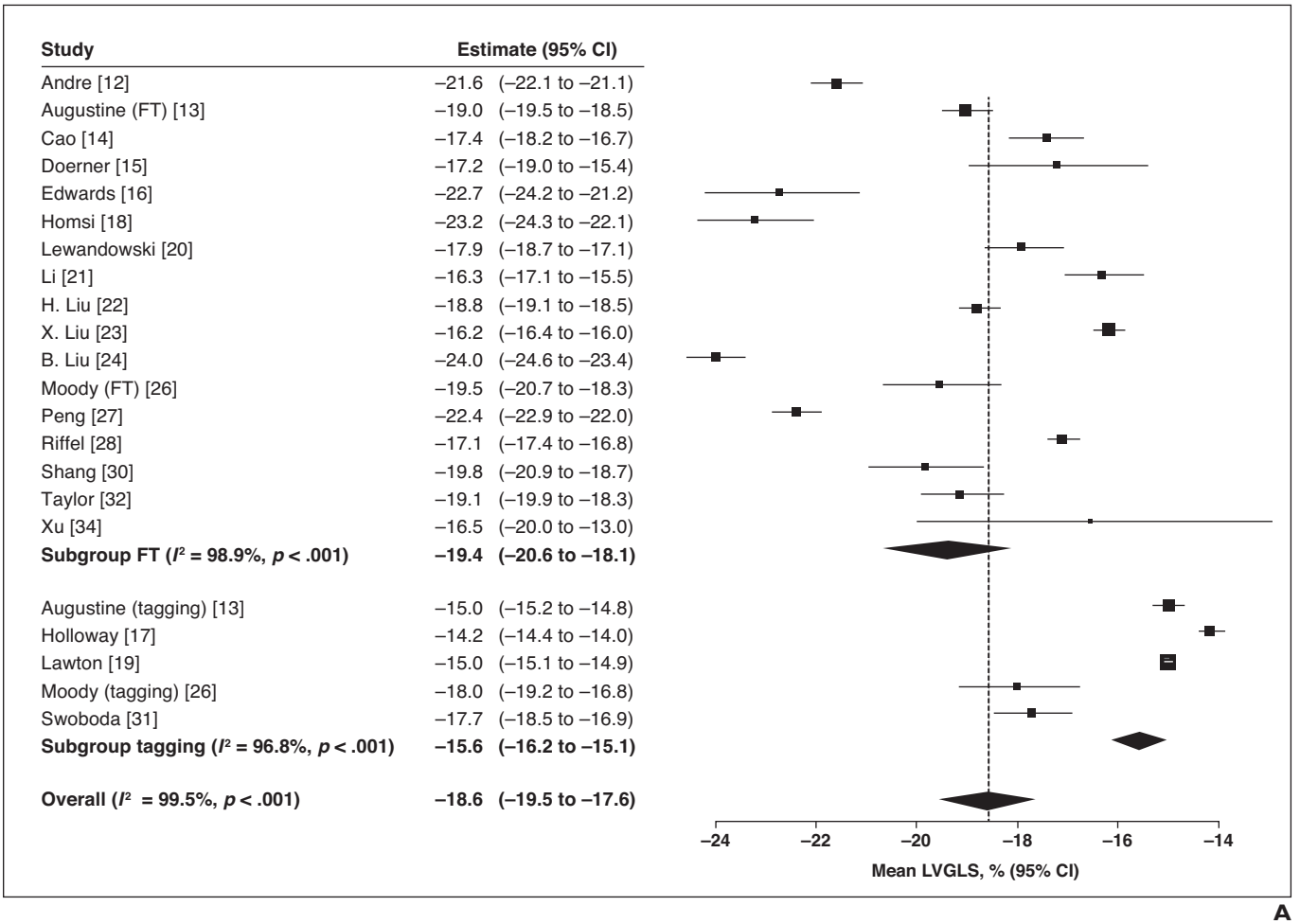


Fig. 2—Forest plots show pooled estimates of left ventricular global longitudinal strain (LVGLS) by feature tracking (FT) or tagging technique and overall. Squares indicate LVGLS value of individual studies, horizontal lines indicate 95% CI of individual studies, dashed vertical line shows pooled mean, and diamonds denote summary values by subgroup and overall with 95% CIs.
A, Mean LVGLS.

(Fig. 2 continues on next page)

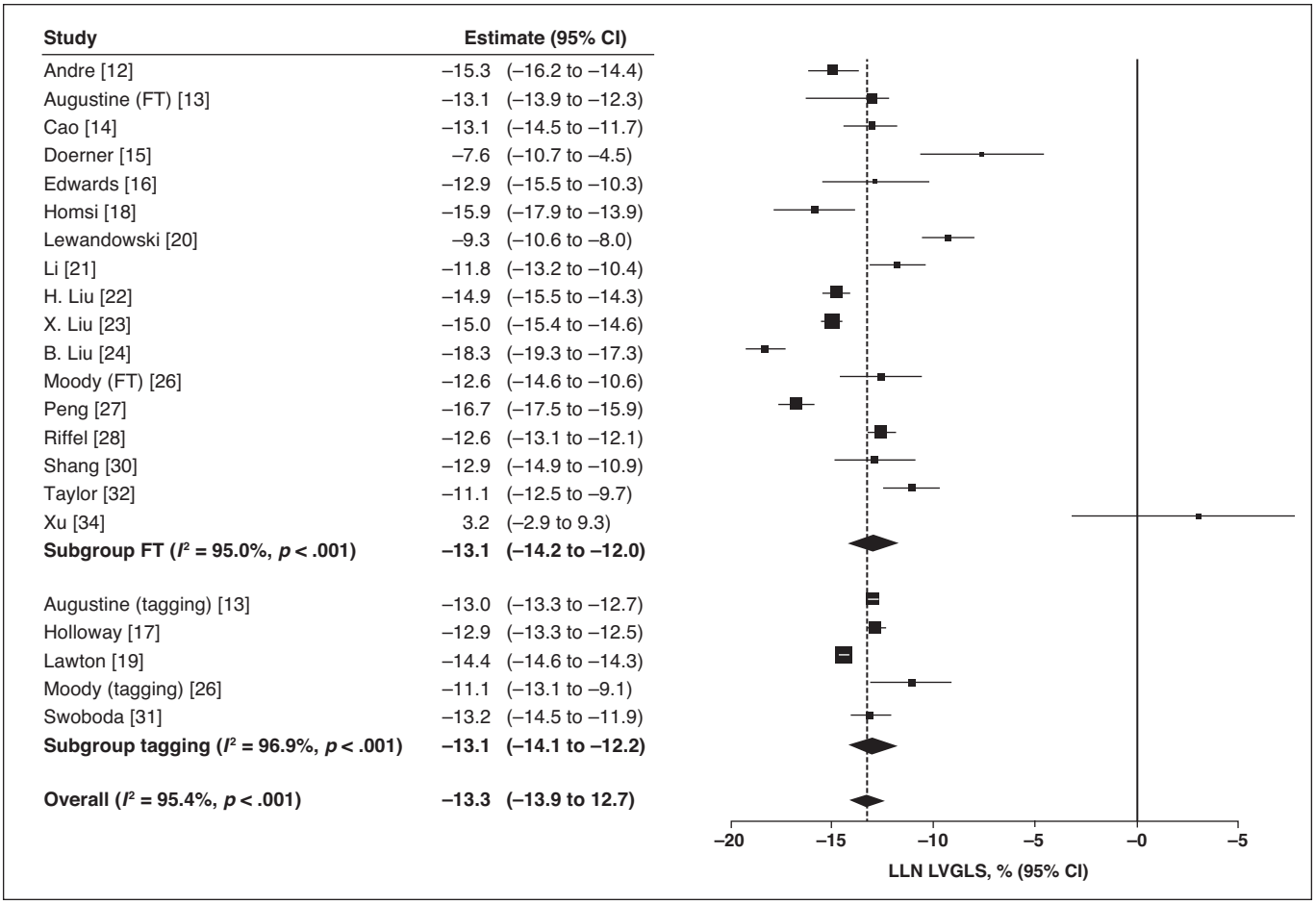


Fig. 2 (continued)—Forest plots show pooled estimates of left ventricular global longitudinal strain (LVGLS) by feature tracking (FT) or tagging technique and overall. Squares indicate LVGLS value of individual studies, horizontal lines indicate 95% CI of individual studies, dashed vertical line shows pooled mean, and diamonds denote summary values by subgroup and overall with 95% CIs.
B, Lower limit of normal (LLN) LVGLS.

in Table 3. Across all studies, pooled LVGLS mean and LLN were –18.6% (95% CI, –19.5% to –17.6%) and –13.3% (–13.9% to 12.7%), respectively (Fig. 2). Pooled LVGCS mean and LLN were –21.0% (95% CI, –22.4% to –19.6%) and –15.6% (–17.0% to –14.3%) (Fig. 3). Pooled LVGRS mean and LLN were 38.7% (95% CI, 30.5–46.9%) and 20.6% (15.1–26.1%) (Fig. 4). Significant heterogeneity was observed for all the pooled analyses performed on testing. Funnel plots are illustrated in Figure 5. Egger test intercepts were –2.35 (p = .12) for pooled LVGLS mean and 1.89 (p = .16) for pooled LVGLS LLN, suggesting no significant publication bias.

Pooled Analyses by Strain Measurement Method

For different MRI measurements of LVGLS, 17 studies of FT and five studies of tagging were evaluated. For FT, pooled LVGLS mean and LLN were –19.4% (95% CI, –20.6% to –18.1%) and –13.1% (–14.2% to –12.0%). For tagging, pooled LVGLS mean and LLN were –15.6% (95% CI, –16.2% to –15.1%) and –13.1% (–14.1% to 12.2%). Other subgroup analyses findings by MRI methods are presented in Table 4.

Only one study had at least 30 healthy patients for DENSE, and no study had at least 30 patients for SENC. However, two [35, 36] and five [37–41] studies had at least 10 healthy patients for DENSE and SENC, respectively. The characteristics of these seven studies are shown in Tables S2 and S3, which can be viewed in the *AJR* electronic supplement to this article at www.ajronline.org.

For DENSE, pooled LVGLS mean and LLN were –12.5% (95% CI, –14.0% to –10.9%) and –7.2% (–9.5% to –5.0%). For SENC, pooled LVGLS mean and LLN were –20.3% (95% CI, –21.2% to –19.4%) and –17.8% (–19.0% to –16.6%) (Table S4 and Fig. S1, which can be viewed in the *AJR* electronic supplement to this article at www.ajronline.org).

Meta-Regression

Meta-regression analysis results for LVGLS mean and LLN for all studies, studies of FT, and studies of tagging are shown in Table 5. A later year of publication, increasing patient age, and increasing BMI were associated with lower (more negative) LVGLS mean values, whereas increasing LVEDVI was associated with higher (less

TABLE 4: Pooled Estimates of LVGLS of All Studies and Subgroups of Studies

Subgroup	No. of Studies	No. of Patients	Mean LVGLS (%)		LLN LVGLS (%)	
			Value	95% CI	Value	95% CI
All studies	22	1769	–18.6	–19.5 to –17.6	–13.3	–13.9 to 12.7
Measurement method						
FT	17	1455	–19.4	–20.6 to –18.1	–13.1	–14.2 to –12.0
Tagging	5	314	–15.6	–16.2 to –15.1	–13.1	–14.1 to –12.2
Software (FT)						
2DCPA[a]	6	732	–19.1	–21.3 to –17.4	–12.5	–14.2 to –10.8
Diogenes[a]	3	178	–20.3	–22.3 to –18.4	–13.9	–14.8 to –13.1
cvi42[b]	6	265	–17.9	–19.8 to –16.1	–12.8	–15.1 to –10.6
MRI scanner vendor						
Siemens Healthcare	17	1279	–18.3	–19.4 to –17.3	–13.3	–14.0 to –12.6
Philips Healthcare	5	490	–19.4	–21.9 to –16.9	–13.3	–15.0 to –11.5
MRI scanner field strength						
1.5 T	14	1282	–19.0	–20.3 to –17.8	–13.1	–14.0 to –12.3
3 T	6	298	–17.1	–18.6 to –15.5	–13.0	–14.2 to –11.7
Long-axis views						
Multiplanar	11	1094	–18.6	–20.1 to –17.0	–12.7	–14.3 to –11.2
Four-chamber only	10	615	–18.9	–21.3 to –16.6	–13.4	–14.4 to –12.4

Note—LVGLS = left ventricular global longitudinal strain, LLN = lower limit of normal, FT = feature tracking, 2DCPA = 2D cardiac performance analysis.
[a]TomTec Imaging Systems.
[b]Circle Cardiovascular Imaging.

negative) LVGLS mean values. Tagging was associated with a less negative mean LVGLS than was FT. There were no significant interactions between LVGLS mean or LLN and year of publication, sex, region, BMI, HR, LVEF, LVEDVI, and MRI vendor. None of the clinical and MRI factors were associated with LVGLS LLN for the overall studies, studies of FT, or studies of tagging except year of publication for studies of tagging.

Interpretation of Reference Ranges

Given the lack of influence of patient and MRI factors on the pooled LLNs and their 95% CIs for LV strain, pooled LLNs and their 95% CIs may be used to define boundaries for normal strain values. For example, the pooled estimate of the LLN for LVGLS based on the meta-analysis is –13.3%. The 95% CI for this estimate is –13.9% to 12.7%. Thus, strain values less negative than 12.7% are most likely abnormal, and strain values more negative than –13.9% are most likely normal. Strain values within 95% CI of LLN (i.e., between –13.9% and 12.7%) are appropriately considered borderline. These interpretations to define reference ranges on the basis of the LLNs and their 95% CI can be applied to LVGCS and LVGRS in a similar manner.

Discussion

In this study, we provide new quantitative thresholds for classifying MRI-derived LV strain measurements using different MRI techniques. The pooled mean value of the MRI-derived LVGLS of –18.6% (95% CI, –19.5% to –17.6%) is similar to the results of prior meta-analyses of LV strain measurements using MRI of –20.1% (95% CI, –20.9% to –19.3%) and echocardiography of –19.7% (95% CI, –20.4% to –18.9%) [6, 10]. However, by including studies with healthy patients, our meta-analysis overcomes the limitations of prior meta-analyses and allows us to further define reference ranges for strain measurements in healthy patients. These ranges in turn facilitate classification of MRI-derived LV strain measurements as normal, borderline, or abnormal using the pooled LLN and 95% CI that we computed. Guidelines currently do not provide recommendations for the reference ranges of normal MRI-derived strain values but may incorporate our findings in the future. On the basis of this classification, patients who have borderline or abnormal strain may be considered for ongoing surveillance, cardiovascular risk factor control, or treatment.

The pooled mean LVGLS and LVGCS were both significantly different between FT and tagging (e.g., for LVGLS, –19.4% for FT and –15.6% for tagging); these results suggest that FT and tagging techniques reflect different physical phenomena. Indeed, these LV strain techniques differ substantially in strain quantification approaches, datasets used, and assumptions made. Tagging uses selective radiofrequency to affect the myocardial magnetization in multiple thin tag planes applied during diastole, with the displacement of the hypointense tagged lines through systole modeling myocardial deformation [42]. On the other hand, FT uses SSFP cine images and aims to track myocardial voxels from one frame to another to ana-

lyze motion in different directions [43]. Normal strains were more variable for FT than for tagging, leading to similar LLNs for LVGLS for the two techniques despite the difference in pooled mean values. The much larger differences in LVGRS between FT and tagging are expected given that measurement of LVGRS requires accurate strain assessment across the span of myocardial thickness from epicardium to endocardium; this does not occur for tagging given the large size and limited spatial resolution of the tags [3].

We also assessed two emerging strain measurement techniques—SENC and DENSE—that reflect distinct physical phenomena as well. These techniques provided different values for mean strain and LLNs compared with FT, tagging, and each other. SENC imaging applies tags as a series of planes in the through-plane direction (as opposed to lines in the in-plane direction of traditional tagging), which causes a change in the position of the peak spectrum in k-space [44]; strain is derived from the rate of this shift in position. DENSE encodes the phase of each voxel in the image to produce a displacement map to calculate myocardial strain in different directions and layers [45]. The SENC method in particular may be sufficiently precise and robust to detect subclinical cardiac dysfunction given the very small gap between pooled LVGLS mean (–20.3%) and LLN (–17.8%), which reflects high agreement and reproducibility [44]. Although direct comparisons were not made, our pooled means of MRI-derived LV global strains for FT and SENC were similar to echocardiography-derived LVGLS values in previous meta-analyses [9, 10]. Further studies of both DENSE and SENC techniques are necessary to optimally determine means and LLNs in healthy individuals for clinical practice.

The strain measurement technique was the only MRI factor associated with pooled LVGLS mean values. Thus, if the same strain measurement technique is used, then strain values for a given patient should remain similar for MRI examinations performed at different centers. Further, pooled LVGLS LLN was not associated with any MRI factor including strain measurement technique (FT or tagging). Therefore, the threshold for borderline and abnormal strain is interchangeable between MRI examinations even across these two techniques.

In meta-regression across all eligible studies, several study and patient factors were associated with pooled mean MRI-derived LVGLS, although no factors were associated with pooled LLN of

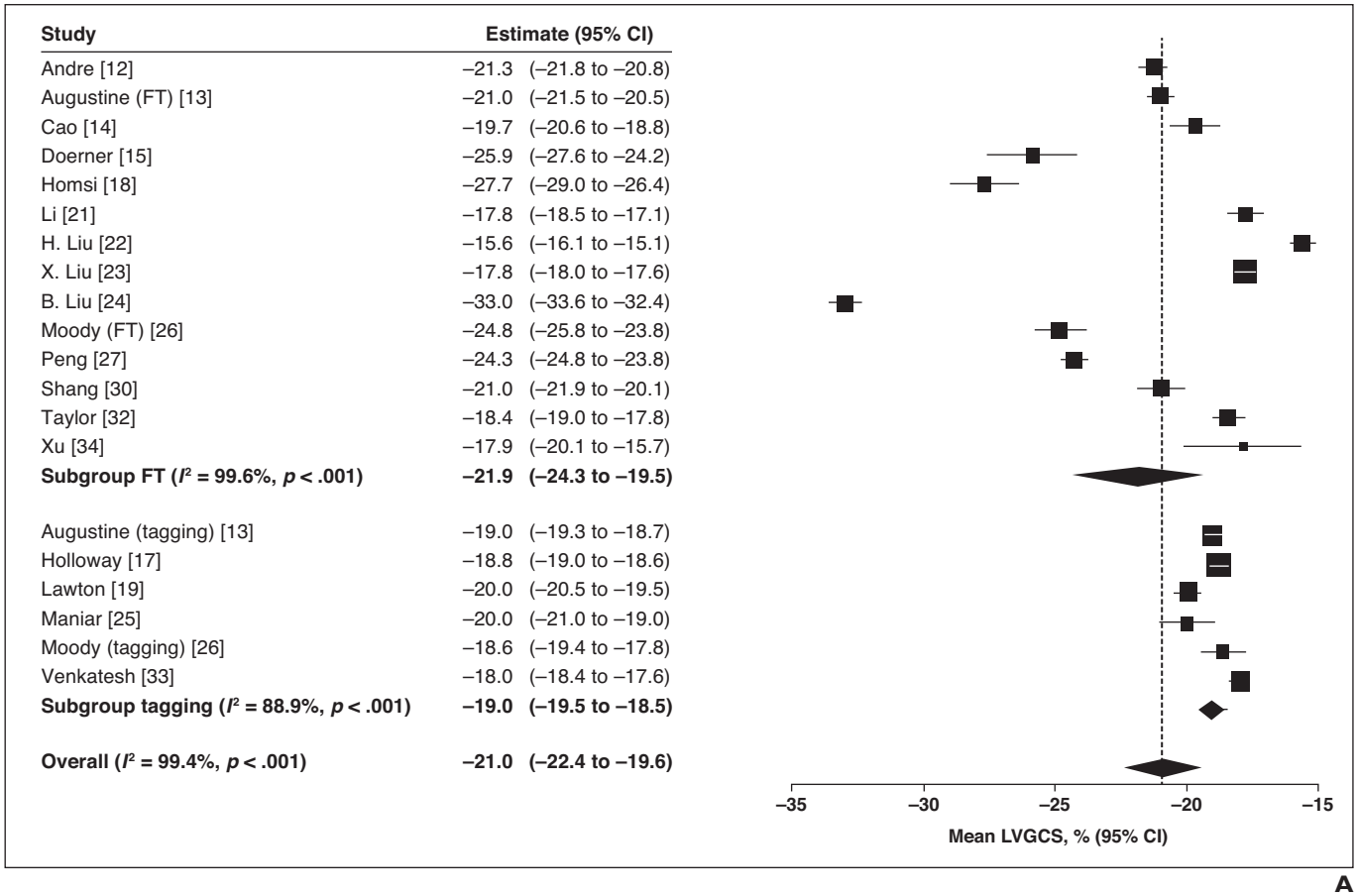


Fig. 3—Forest plots show pooled estimates of left ventricular global circumferential strain (LVGCS) by feature tracking (FT) or tagging technique and overall. Squares indicate LVGCS value of individual studies, horizontal lines indicate 95% CI of individual studies, dashed vertical line shows pooled mean, and diamonds denote summary values by subgroup and overall with 95% CIs.
A, Mean LVGCS.

(Fig. 3 continues on next page)

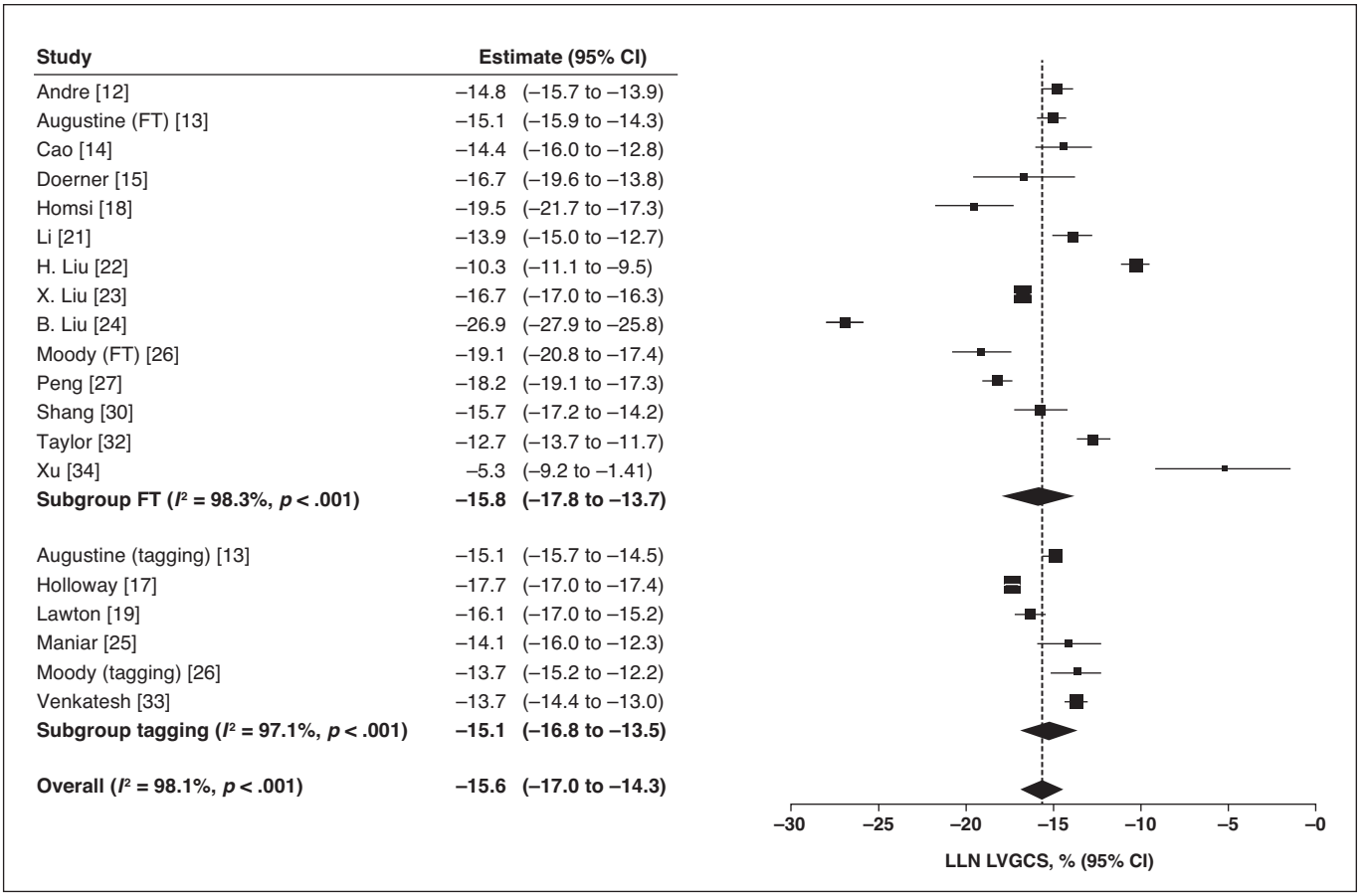


Fig. 3 (continued)—Forest plots show pooled estimates of left ventricular global circumferential strain (LVGCS) by feature tracking (FT) or tagging technique and overall. Squares indicate LVGCS value of individual studies, horizontal lines indicate 95% CI of individual studies, dashed vertical line shows pooled mean, and diamonds denote summary values by subgroup and overall with 95% CIs.
B, Lower limit of normal (LLN) LVGCS.

LVGLS. More recently published studies reported mean LVGLS values that were more negative, in part because all of the tagging studies, which had a less negative mean LVGLS, were published in 2016 or earlier. Higher mean patient age was associated with a more negative mean LVGLS (i.e., more deformation), which was not observed in previous meta-analyses of echocardiography-derived LVGLS [9, 10]. It is possible that, given our study's exclusion of patients with risk factors, the older patients in our study were healthier than older patients in the general population. Similarly, higher mean BMI had more negative mean LVGLS, particularly for FT, which also was not reported by previous meta-analyses [9, 10]. Finally, a higher mean LVEDVI was associated with a less negative mean LVGLS, consistent with LV dilatation as one of the first signs of subclinical LV systolic dysfunction. A geometric equation linking LV size, LVGLS, LVGCS, wall thickness, and LVEF was recently devised, although this has not been externally applied to MRI measurements [46].

The study's limitations include heterogeneities in the design and MRI techniques of included studies. To address heterogeneities in study design, we excluded studies with fewer than 30 subjects or those in which men or women represented less than one-third of the sample. To address heterogeneities in MRI technique, we performed additional subgroup and meta-regression analysis. There was underrepresentation, resulting in limited power, for certain subgroups, including older patients and all of the strain measurement techniques except FT. The definition of LLN was based mathematically on the boundary of the 95% CI, consistent with other guideline-recommended chamber quantification parameters, rather than based on prognostic significance [2]. Given that patient-level data were not available, meta-regression analysis was performed using study-level data, and not all variables were reported by all studies. Further, in clinical practice, strain results should not be interpreted in a binary fashion as normal or abnormal given that more abnormal strain values are associated with higher risk of negative outcomes [47]. In addition, we did not evaluate the prognostic implications for the classification, which would require further studies similar to those previously performed for echocardiography [3]. Also, the assessment for risk of bias identified that all studies except one used semiautomated strain software with

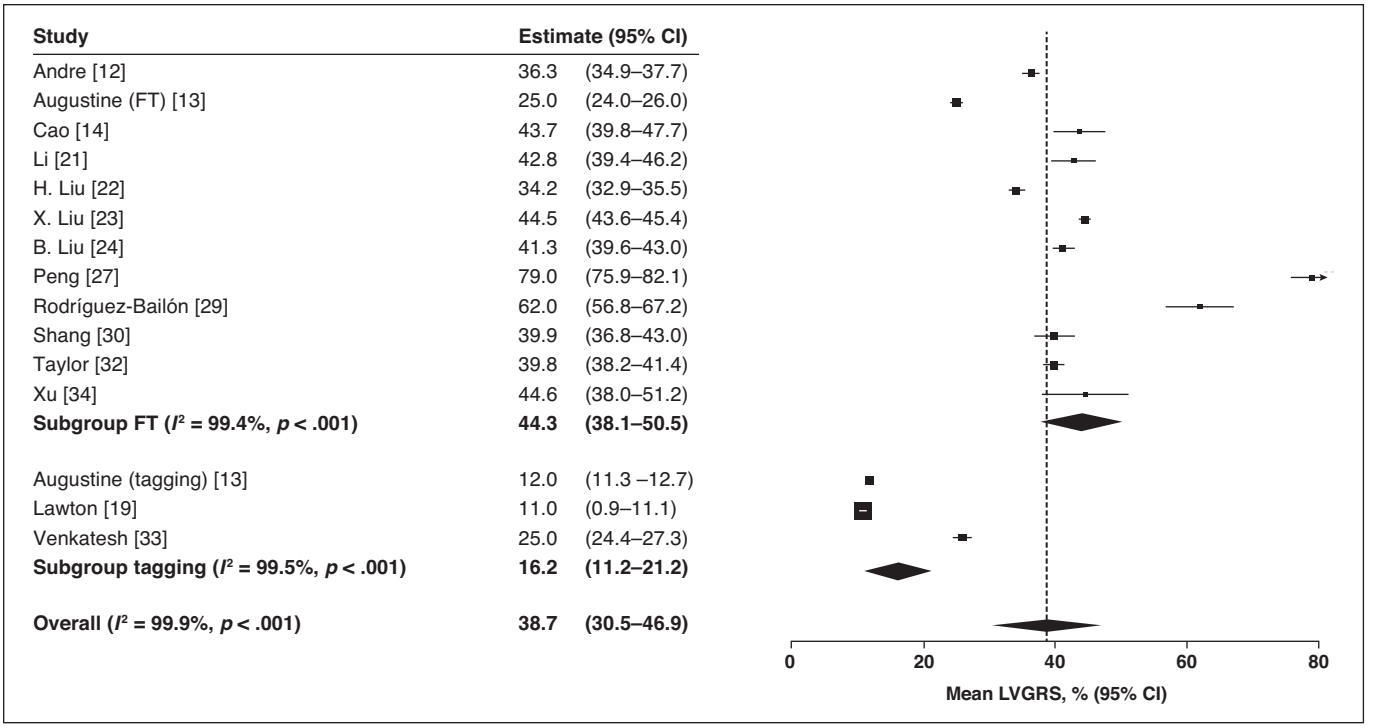
TABLE 5: Meta-Regression of LVGLS Values

LVGLS Value, Factor	All Eligible Studies		FT Studies		Tagging Studies	
	Beta Coefficient (95% CI)	*p*	Beta Coefficient (95% CI)	*p*	Beta Coefficient (95% CI)	*p*
Mean LVGLS						
Year of publication	−0.60 (−1.06 to −0.15)	**.009**	−0.24 (−0.86 to 0.38)	**.45**	−0.70 (−1.15 to −0.24)	**.003**
Age	−0.18 (−0.29 to −0.06)	**.004**	−0.13 (−0.28 to 0.02)	.08	0.03 (−0.22 to 0.27)	.84
Male	0.03 (−0.10 to 0.16)	.63	0.00 (−0.23 to 0.23)	>.99	−0.05 (−0.13 to 0.03)	.12
Asia (vs USA, Australia, and countries in Europe)	0.45 (−2.02 to 2.91)	.72	1.84 (−0.42 to 4.10)	.11	No studies from Asia	
BMI	−1.14 (−2.14 to −0.14)	**.03**	−1.35 (−2.01 to −0.68)	**< .001**	0.73 (−4.93 to 6.39)	.80
SBP	−0.05 (−0.34 to 0.25)	.77	−0.26 (−0.55 to 0.03)	.08	0.14 (−0.03 to 0.32)	.11
DBP	−0.15 (−0.41 to 0.12)	.28	−0.24 (−0.59 to 0.11)	.17	0.17 (0.04–0.31)	**.01**
HR	−0.07 (−0.37 to 0.22)	.62	−0.03 (−0.31 to 0.25)	.83	1.67 (1.26–2.08)	**< .001**
LVEF	−0.18 (−0.43 to 0.07)	.16	−0.29 (−0.53 to −0.04)	**.02**	0.09 (−0.21 to 0.39)	.56
LVEDVI	0.09 (0.01–0.18)	**.03**	0.09 (0.02–0.16)	**.02**	Reported by one study	
LVMI	0.06 (−0.19 to 0.31)	.65	0.04 (−0.21 to 0.28)	.77	−0.09 (−0.38 to 0.21)	.56
Tagging as measurement method (vs FT)	3.44 (1.18–5.71)	**.003**		NR	NR	NR
Philips as MRI scanner vendor (vs Siemens)	1.03 (−1.67 to 3.72)	.46	0.55 (−2.22 to 3.32)	.70	2.29 (−0.31 to 4.88), 0	.08
3-T Field strength (vs 1.5 T)	1.95 (−0.29 to 4.18)	.09	2.28 (−0.01 to 4.59)	.05	0.01 (−2.71 to 2.73), 0	>.99
Long-axis four-chamber view only (vs multiplanar)	−0.40 (−2.69 to 1.89)	.73	−1.06 (−3.41 to 1.30)	.38	−1.55 (−4.90 to 1.81)	.37
LLN LVGLS						
Year of publication	−0.19 (−0.71 to 0.33)	.47	−0.21 (−0.91 to 0.49)	.55	0.64 (0.53–0.76)	**< .001**
Age	−0.03 (−0.17 to 0.12)	.72	−0.03 (−0.22 to 0.16)	.76	0.07 (−0.06 to 0.19)	.31
Male	0.03 (−0.10 to 0.17)	.64	0.04 (−0.16 to 0.23)	.72	0.02 (−0.03 to 0.07)	.47
Asia (vs USA, Australia, and countries in Europe)	0.07 (−2.48 to 2.63)	.96	0.44 (−2.82 to 3.70)	.79	No studies from Asia	
BMI	−0.18 (−1.15 to 0.79)	.72	−0.21 (−1.29 to 0.88)	.71	0.13 (−0.53 to 0.80)	.70
SBP	−0.02 (−0.15 to 0.12)	.82	−0.06 (−0.28 to 0.16)	.60	0.02 (−0.10 to 0.13)	.76
DBP	−0.07 (−0.20 to 0.05)	.26	−0.11 (−0.25 to 0.04)	.14	−0.01 (−0.13 to 0.12)	.94
HR	0.24 (−0.26 to 0.74)	.34	0.29 (−0.27 to 0.85)	.31	−0.10 (−0.81 to 0.63)	.80
LVEF	−0.11 (−0.41 to 0.19)	.47	−0.19 (−0.59 to 0.21)	.36	0.03 (−0.04 to 0.11)	.39
LVEDVI	0.01 (−0.09 to 0.10)	.91	0.01 (−0.10 to 0.11)	.89	Reported by one study	
LVMI	0.18 (−0.01 to 0.36)	.06	0.18 (−0.05 to 0.41)	.13	0.17 (−0.02 to 0.37)	.08
Tagging as measurement method (vs FT)	0.01 (−2.75 to 2.76)	> .99		NR	NR	
Philips as MRI scanner vendor (vs Siemens)	−0.21 (−3.02 to 2.60)	.88	−0.15 (−3.53 to 3.23)	.93	0.00 (−2.12 to 2.11)	> .99
3-T Field strength (vs 1.5 T)	0.58 (−1.83 to 2.99)	.64	1.21 (−2.08 to 4.49)	.47	0.36 (−1.05 to 1.77)	.61
Long-axis four-chamber view only (vs multiplanar)	0.31 (−2.17 to 2.79)	.81	0.05 (−3.26 to 3.36)	.98	0.13 (−0.32 to 0.59)	.56

Note—Boldface type indicates statistically significant difference ($p < .05$). LVGLS = left ventricular global longitudinal strain, FT = feature tracking, BMI = body mass index (weight in kilograms divided by the square of height in meters), SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, LVEF = left ventricular ejection fraction, LVEDVI = left ventricular end-diastolic volume index, LVMI = left ventricular mass index, NR = not reported, Philips = Philips Healthcare, Siemens = Siemens Healthcare, LLN = lower limit of normal.

manual tracing. Although manual tracing is associated with observer bias, this approach reflects current standard practice for MRI-derived chamber quantification. Finally, publication bias is a potential limitation of all meta-analyses. However, it is likely less of a limitation for our study exploring normal ranges in healthy subjects than it would be for studies exploring the role of strain measurements in predicting outcomes or comparing treatment effects on these measurements.

In conclusion, this meta-analysis provided the pooled means and LLNs, along with corresponding 95% CIs, for MRI-derived LVGLS, LVGCS, and LVGRS in healthy patients. The pooled LLNs and their 95% CIs serve as reference ranges that allow LV strain to



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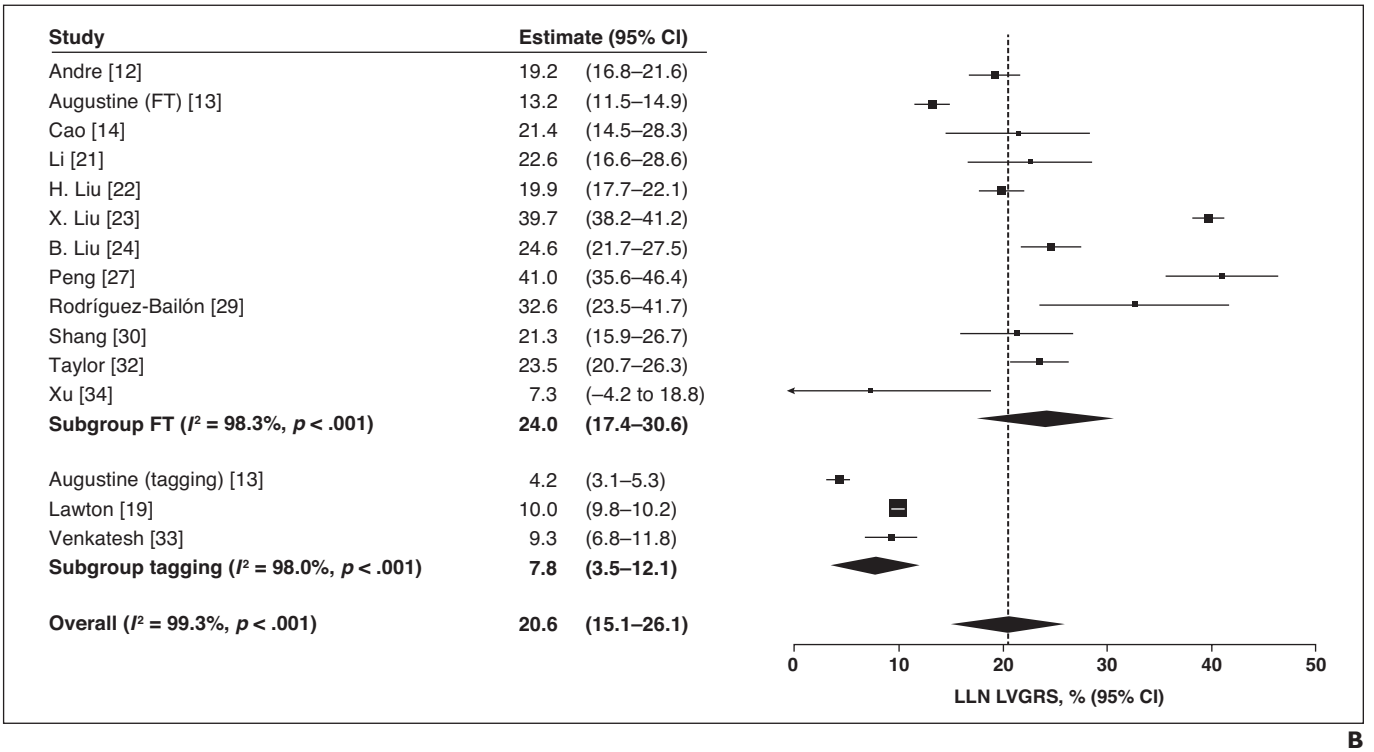

B

Fig. 4—Forest plots show pooled estimates of left ventricular global radial strain (LVGRS) by feature tracking (FT) or tagging technique and overall. Squares indicate LVGRS value of individual studies, horizontal lines indicate 95% CI of individual studies, dashed vertical line shows pooled mean, and diamonds denote summary values by subgroup and overall with 95% CIs.
A, Mean LVGRS.
B, Lower limit of normal (LLN) LVGRS.

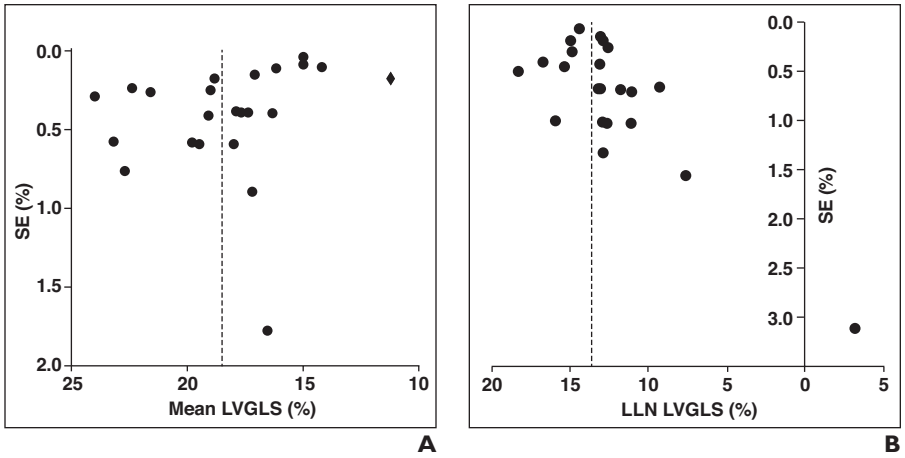

Fig. 5—Funnel plots of pooled estimates of left ventricular global longitudinal strain (LVGLS) to assess for publication bias show results suggesting no significant publication bias. Vertical line shows pooled mean. SE = standard error.
A, Pooled estimates of mean LVGLS.
B, Pooled estimates of lower limit of normal (LLN) LVGLS.

be classified as normal, borderline, or abnormal. Various explored factors affected mean LVGLS but did not affect the LLN. This study lays the foundation for future clinical adoption of MRI-derived LV strain in both healthy patients and patients with various disease states, with the potential to guide management decisions.

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(Editorial Comment starts on next page)

Editorial Comment: Why Systematic Review and Meta-Analysis to Define Normal Ranges May Be the Best Way Right Now to Translate Cardiac MRI Strain Analysis Into Everyday Practice

Large multicenter randomized clinical trials provide high-level evidence but are sometimes impractical (e.g., low disease prevalence). Just-in-time critical evidence appraisal is unrealistic in busy medical practices. Patient-tailored test selection and treatment prescription require quick and flexible thinking, so referring clinicians rely on heuristics, empirical evidence, and the expertise of consultants, including cardiac radiologists, who in turn make specialty-specific decisions.

Left ventricular (LV) strain, for example, may be quantified using older MRI methods (tagging or feature tracking [FT]) or newer pulse sequences (displacement encoding with stimulated echoes [DENSE] or strain-encoding [SENC]). Prognostication and clinical management require not only quantifying strain severity, but also reproducibly discriminating thresholds between the lower limit of normal and borderline or minimally abnormal values (subclinical disease). Threshold discrimination, in turn, requires a validated range of normal values in healthy individuals, ideally stratified into cohorts (e.g., age- and sex-based cohorts).

If MRI-derived LV strain normal ranges have not been defined and the reference standard (echocardiography) has worse spatial and contrast resolution than MRI, would you trust the accuracy of your data? If you can't trust your data, neither can referring providers: "What are we to do when the irresistible force of the need to offer clinical advice meets with the immovable object of flawed evidence?" [1].

Systematic review and meta-analysis of the best available evidence (even if imperfect) may currently be the most robust way to select the best MRI LV strain quantification method and fill reference range gaps, which this study does. If we are willing to reference and discuss this evidence, we may soon be able to translate LV strain analysis from the research domain into everyday clinical practice. "All we can do is our best: give the advice, but alert the advisees to the flaws in the evidence on which it is based" [1]. In other words, "don't let the perfect be the enemy of the good" [2].

Julianna M. Czum, MD
Dartmouth-Hitchcock Medical Center
Lebanon, NH
Julianna.M.Czum@Hitchcock.org

The author declares that there are no disclosures relevant to the subject matter of this work.

doi.org/10.2214/AJR.20.25041

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