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Letters

RESEARCH LETTER

Lower Limit of the Reference Normal Range for Left Atrial Strain

A Meta-Analysis

Recent studies using 2-dimensional speckle-tracking transthoracic echocardiography (2D-STE) have highlighted the potential clinical utility of left atrial (LA) global longitudinal reservoir strain (LA strain) in patients with cardiovascular (CV) diseases.[1-3] However, the lower limit of the reference normal range (LLN) for LA strain across different ultrasound software vendors remains undefined. Accordingly, this study performed a meta-analysis to define the LLN of LA strain for each ultrasound software vendor.

A conventional meta-analysis was performed on studies published in PubMed (English language) that analyzed biplane or 4-chamber view (4CH) LA strain using 2D-STE (R-R gating analysis) in healthy adult participants aged ≥18 years with a sample size of ≥120 to avoid biases associated with small sample sizes in determining the LLN. The search process was completed on December 12, 2025. The methodological description of the meta-analysis was registered and published in a prespecified protocol (CRD42018104096).[4]

The following tools were applied to reduce biases and increase the accuracy of the findings of the meta-analysis: 1) studies with a sample size of <120 healthy adult subjects were excluded to avoid biases linked to a small size when determining the LLN; 2) the calculation of the pooled LLN of LA strain for a specific software vendor was avoided when only 1 study for the specific software vendor was published; 3) statistical heterogeneity between studies was analyzed using Cohran's Q test and I^2 statistic test; statistical heterogeneity was not evaluated when fewer than 10 studies were included in the meta-analysis to avoid potential biases associated with the Q test and I^2 test analyses; 4) publication biases were assessed using Egger's test and Begg's test; and 5) analyses of subgroups (sex and age) were performed only in studies with an adequate sample size in the subgroup analyzed (ie, ≥120 healthy adult participants for each subgroup).[4]

Following the recommendations of the European Association of Cardiovascular Imaging and American Society of Echocardiography (ASE) for chamber quantification and given that LA strain regularly has a normal distribution in healthy adults, the LLN of LA strain was calculated as −1.96 SD from the arithmetic mean (ie, mean − [1.96 * SD]). Nonetheless, in the studies that reported a non-normal distribution of LA strain data, the 2.5th percentile was selected to determine the LLN of LA strain. The LLN of LA strain and its 95% CI (± 1.96 * standard error [SE]) was determined for each study, and then the average/pooled LLN of LA strain from all studies for each software vendor was calculated. The SE of the LLN of LA strain from each study was calculated as the square root of ($[3*SD^2]$/sample size).

For the meta-analysis, the generic inverse variance method was used to determine the pooled LLN of LA strain and its 95% CI, and a random effect model was selected to avoid bias if the data had significant heterogeneity. A fixed-effect model was selected if it was not possible to evaluate heterogeneity between studies (ie, fewer than 10 studies included in the meta-analysis). Moreover, an average LLN with the SE of the fixed-effect model from all studies was determined when different methodologies were used in the determination of the LLN for LA strain (ie, mean −1.96 SD and 2.5th percentile) across the studies.

Continuous data were presented as mean ± SD and dichotomous data as percentages. Values of LA strain were reported in absolute values and strain units. Differences were considered statistically significant when $P < 0.05$. MedCalc Statistical Software (version 23.3; MedCalc Software) was used to analyze the data. The institutional review board approved the data analysis.

The meta-analysis, comprising a total of 13,472 healthy adults from 23 studies, identified the LLN of LA strain at 23% (95% CI: 22%-25%) across various ultrasound software vendors, including EchoPac (GE Vingmed Ultrasound; GE HealthCare), TomTec (TomTec), and QLab (Philips) (**Table 1**). Differences in the LLN of LA strain among these software vendors were neither clinically relevant (relative differences < 10%) nor statistically significant ($P > 0.05$). Data from studies including large cohorts of healthy adults (ie, sample size ≥120) were limited (ie, only 1 study) for other software vendors, such as Echoinsight-Epsilon (Epsilon) and Us2.ai, or absent (ie, no studies) for vendors including Toshiba/Canon

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TABLE 1 Meta-Analysis of the LLN of LA Global Longitudinal Reservoir Strain (LA Strain)

						LA Strain			
First Author, Year	**Sample Size**	**Age, y**	**Women**	**Country**	**Software Vendor**	**Biplane**	**LLN**	**4CH**	**LLN**
Sun et al, 2013[a]	121	47 ± 15	59	China	EchoPac (NA)	46.7 ± 7.8	31.4	46.4 ± 10.5	25.8
Yang et al, 2014	152	48 ± 8	70	South Korea	EchoPac (NA)	NA	NA	38.0 ± 7.4	23.5
Xu et al, 2015[a]	124	51 ± 11	63	China	EchoPac (NA)	47.0 ± 8.8	29.7	46.5 ± 10.7	25.5
Morris et al, 2015[a]	329	36 ± 12	153	Japan and Germany	EchoPac (v 113)	45.5 ± 11.4	23.1	44.6 ± 12.8	23.0[b]
Liao et al, 2017[a]	2,812	47 ± 9	976	Taiwan	EchoPac (v 10.8)	38.4 ± 8.0	22.7	38.3 ± 8.1	22.4
Brand et al, 2018	190	42 ± 10	190	Germany	EchoPac (v 113)	NA	NA	43.9 ± 8.5	27.2
Sun et al, 2020[a]	324	49 ± 16	167	South Korea	EchoPac (v 201)	35.9 ± 10.6	18.9[b]	35.4 ± 11.3	17.2[b]
Bhatt et al, 2021[a]	131	44 ± 15	62	USA	EchoPac (v 203)	37.0 ± 8.0	21.3	36.0 ± 9.0	18.4
Stefani et al, 2021[a]	147	44 ± 14	69	Australia	EchoPac (v 203)	35.2 ± 6.9	21.7	34.3 ± 7.4	19.8
Nielsen et al, 2021[a]	1,641	45 ± 15	1,025	Denmark	EchoPac (v 202)	40.7 ± 11.1	23.0[b]	40.6 ± 13.4	21.3[b]
Nyberg et al, 2023[a]	1,194	57 ± 12	662	Norway	EchoPac (v 204)	33.0 ± 8.3	16.7	32.6 ± 8.5	15.9
Solberg et al, 2024[a]	758	63 ± 0.7	433	Norway	EchoPac (v 202-203)	NA	NA	36.5 ± 9.3	21.9[b]
Results: EchoPac: N = 7,923; pooled (average) LLN = biplane 23.1 (95% CI: 22.7-23.4); 4CH 21.8 (95% CI: 21.4-22.1)									
Meel et al, 2017	120	38 ± 12	60	South Africa	aCMQ	39.0 ± 8.3	22.7	NA	NA
Van Grootel et al, 2018[a]	129	44 ± 13	74	Netherlands	aCMQ	39.6 ± 6.3	27.2	40.2 ± 7.3	25.8
Peng et al, 2023	151	40 ± 11	72	China	aCMQ	NA	NA	37.6 ± 9.9	18.2
Results: Philips QLab (aCMQ)[c]: N = 400; pooled LLN = biplane 25.6 (95% CI: 24.1-27.1); 4CH 22.8 (95% CI: 21.1-24.6)									
Sugimoto et al, 2018[a]	371	34-55	206	Europe and USA	2D-CPA	42.9 ± 9.3	24.6	41.4 ± 10.4	20.9
Yoshida et al, 2019[a]	481	60 ± 12	260	Japan	2D-CPA	40.4 ± 6.9	26.8	40.7 ± 8.0	25.0
Mutluer et al, 2022	121	43 ± 13	67	Netherlands	2D-CPA	NA	NA	36.3 ± 11.0	14.7
Singh et al, 2022	1,765	47 ± 17	864	Mixed	2D-CPA	NA	NA	42.1 ± 10.0	22.5
Pugliese et al, 2022[a]	155	65 ± 11	62	Italy	2D-CPA	38.3 ± 5.1	28.3	39.3 ± 4.5	30.4
Chen et al, 2023[a]	156	42 ± 13	90	Australia	2D-CPA	32.3 ± 4.2	24.0	NA	NA
Results: TomTec 2D-CPA[d]: N = 3,049; pooled LLN = biplane 25.9 (95% CI: 25.3-26.6); 4CH 24.3 (95% CI: 23.7-24.8)									
Inciardi et al, 2022	301	74 ± 4	197	USA	AutoStrain	NA	NA	36.2 ± 6.6	23.2
Peng et al, 2023	151	40 ± 11	72	China	AutoStrain	NA	NA	48.0 ± 10.0	28.4
Dong et al, 2025	1,648	44 ± 14	938	China	AutoStrain	NA	NA	41.3 ± 10.9	19.9
Results: TomTec/Philips AutoStrain[e]: N = 2,100; pooled LLN = biplane NA; 4CH 21.5 (95% CI: 20.8-22.2)									

Values are mean ± SD or n. LA strain values and LLN are shown in strain units (ie, %). References of the studies included in the meta-analysis: Sun et al, *Int J Cardiol*. 2013;168(4):3473-3479; Yang et al, *J Hypertens*. 2014;32(9):1862-1869; Xu et al, *Medicine (Baltimore)*. 2015;94(6):e526; Morris et al, *Eur Heart J Cardiovasc Imaging*. 2015;16(4):364-372; Liao et al, *Circ Cardiovasc Imaging*. 2017;10(10):e006077; Brand et al, *Echocardiography*. 2018;35:1542-1549; Sun et al, *J Cardiovasc Imaging*. 2020;28(3):186-198; Bhatt et al, *Am J Physiol Heart Circ Physiol*. 2021;320(2):H575-H583; Stefani et al, *Echocardiography*. 2021;38(3):417-426; Nielsen et al, *Eur Heart J Cardiovasc Imaging*. 2021;23(1):42-51; Nyberg et al, *JACC Cardiovasc Imaging*. 2023;16(12):1516-1531; Solberg et al, *Echocardiography*. 2024;41(6):e15852; Meel et al, *Eur Heart J Cardiovasc Imaging*. 2017;18(3):350-355; Van Grootel et al, *Echocardiography*. 2018;35:1956-1965; Peng et al, *Cardiovasc Ultrasound*. 2023;21(1):12; Sugimoto et al, *Eur Heart J Cardiovasc Imaging*. 2018;19(6):630-638; Yoshida et al, *J Am Coll Cardiol*. 2019;74(14):1789-1800; Mutluer et al, *Eur Heart J Open*. 2022;2(3):oeac023; Singh et al, *J Am Soc Echocardiogr*. 2022;35(2):154-164.e3; Pugliese et al, *JACC Cardiovasc Imaging*. 2022;15(9):1545-1559; Chen et al, *Int J Cardiol Cardiovasc Risk Prev*. 2023:19:200211; Inciardi et al, *J Am Coll Cardiol*. 2022;79(16):1549-1561; Peng et al, *Cardiovasc Ultrasound*. 2023;21(1):12; Dong et al, *J Am Soc Echocardiogr*. 2025;38(9):794-803. [a]Indicates requested data. [b]Indicates 2.5th percentile. [c]The aCMQ (automated Cardiac Motion Quantification) software package from QLab software is from Philips. [d]The 2D-CPA, 2-Dimensional Cardiac Performance Analysis software package is from TomTec (software vendor). [e]The AutoStrain software is an automated measurement package for LA strain developed by TomTec. It is also incorporated as an optional feature in newer versions (12-14) of the QLab software from Philips. This AutoStrain package, provided by TomTec and integrated into recent QLab versions, differs from the conventional strain analysis used by TomTec (2D-CPA) and QLab (aCMQ) because it employs a distinct algorithm to calculate LA strain.

2D-CPA = 2-dimensional cardiac performance analysis; 4CH = 4-chamber view; aCMQ = automated cardiac motion quantification; LA = left atrial; LA strain = left atrial longitudinal reservoir strain obtained from the average of all LA segments in the apical 4 and 2-chamber views (biplane) or only 4CH using R-R gating analysis and 2D-STE; LLN = lower limit of the reference normal range; NA = not available; v = version.

UltraExtend (Toshiba/Canon), Siemens Syngo VVI (Siemens), Esaote 2D X-Strain (Esaote), Hitachi/Fujifilm (Hitachi Medical Systems and Fujifilm), Mindray, Samsung (Samsung Healthcare), Medis Suite (Medis), Caas Qardia (Pie Medical Imaging), Ultromics, and DiA Imaging Analysis, precluding calculation of a pooled LLN of LA strain for these vendors. Similarly, for the subgroup analyses by sex and age, few studies (and only those using EchoPac and TomTec) had sufficiently large and appropriate sample sizes (ie, ≥120 healthy adults per subgroup) to define and compare pooled LLN values for women versus men and for younger versus older subjects. Nonetheless, small relative differences (<10%) with respect to the LLN of LA strain at 23% were observed between age and sex groups across most studies and in the largest studies. The studies included in the meta-analysis were of adequate methodological quality, showed no significant publication bias, and exhibited heterogeneity primarily attributable to differences in sample size.

In clinical practice, knowledge of the specific cutoff that defines normal or abnormal cardiac function is of key importance for clinical decision-making and for evaluating CV risk in individual patients. For conventional LA parameters, such as the LA volume index, a well-validated cutoff exists to define normal or abnormal LA size and to predict CV risk (ie, LA volume index >34 mL/m^2). However, important issues remain regarding LA strain, including the lack of a validated definition of normal or abnormal LA strain and uncertainty as to whether variability among different ultrasound software vendors may influence the definition of normal or abnormal LA strain. In our present study, a large meta-analysis of 13,472 healthy adults, the LLN of LA strain for the most commonly used ultrasound software vendors (ie, EchoPac, TomTec, and QLab) was 23%, which was consistent with the LLN of LA strain recently recommended by the ASE Consensus for Clinical Applications of Strain.[5] Therefore, the large dataset presented in this meta-analysis supports the use of a cutoff at 23% as an appropriate threshold to define normal or abnormal LA strain in daily clinical practice.

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