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ORIGINAL ARTICLE

Left atrial reservoir strain is a superior discriminator of cardioembolism in ischaemic stroke

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Abstract

Aims

Echocardiographic measures of left heart size and function have long been associated with cardioembolic mechanisms of stroke development, however, the diagnostic performance and comparison of measures of atrial function in this context has not been well studied. We sought to evaluate the diagnostic performance of left atrial reservoir strain (LASr) in identification of cardioembolism in the ischaemic stroke population relative to traditional measures of left heart size and function.

Methods and results

Consecutive patients admitted to our institution with ischaemic stroke or transient ischaemic attack were recruited and underwent comprehensive transthoracic echocardiography. Strokes were classified by aetiology with comparison undertaken between cardioembolic and non-cardioembolic types. Four hundred and eighteen consecutive stroke patients with a cardioembolic ($n = 229$) or non-cardioembolic ($n = 189$) stroke aetiology were analysed. LASr was impaired in cardioembolic compared with non-cardioembolic strokes ($16.7 \pm 8.2\%$ vs. $26.0 \pm 5.5\%$, $P < 0.01$) and provided greatest discrimination [area under the curve (AUC) 0.813, 95%CI 0.773–0.858] in differentiating stroke subtypes when compared with LVEF (AUC difference 0.150, $P < 0.01$), LAVI (AUC difference 0.083, $P < 0.01$), and E/e' (AUC difference 0.163, $P < 0.01$). Inclusion of LASr in a model with conventional left heart echocardiographic factors improved model performance with a net reclassification improvement of 1.083 (95%CI 0.945–1.220, $P < 0.01$). Further, a proposed user-defined model-based clinical algorithm with LASr demonstrated improved diagnostic accuracy of the identification of cardioembolic stroke subtypes which was best appreciated in patients without atrial fibrillation.

Conclusion

LASr may provide enhanced diagnostic accuracy beyond conventional echocardiographic measures to discriminate cardioembolic from non-cardioembolic stroke mechanisms, in particular amongst those without comorbid atrial fibrillation.

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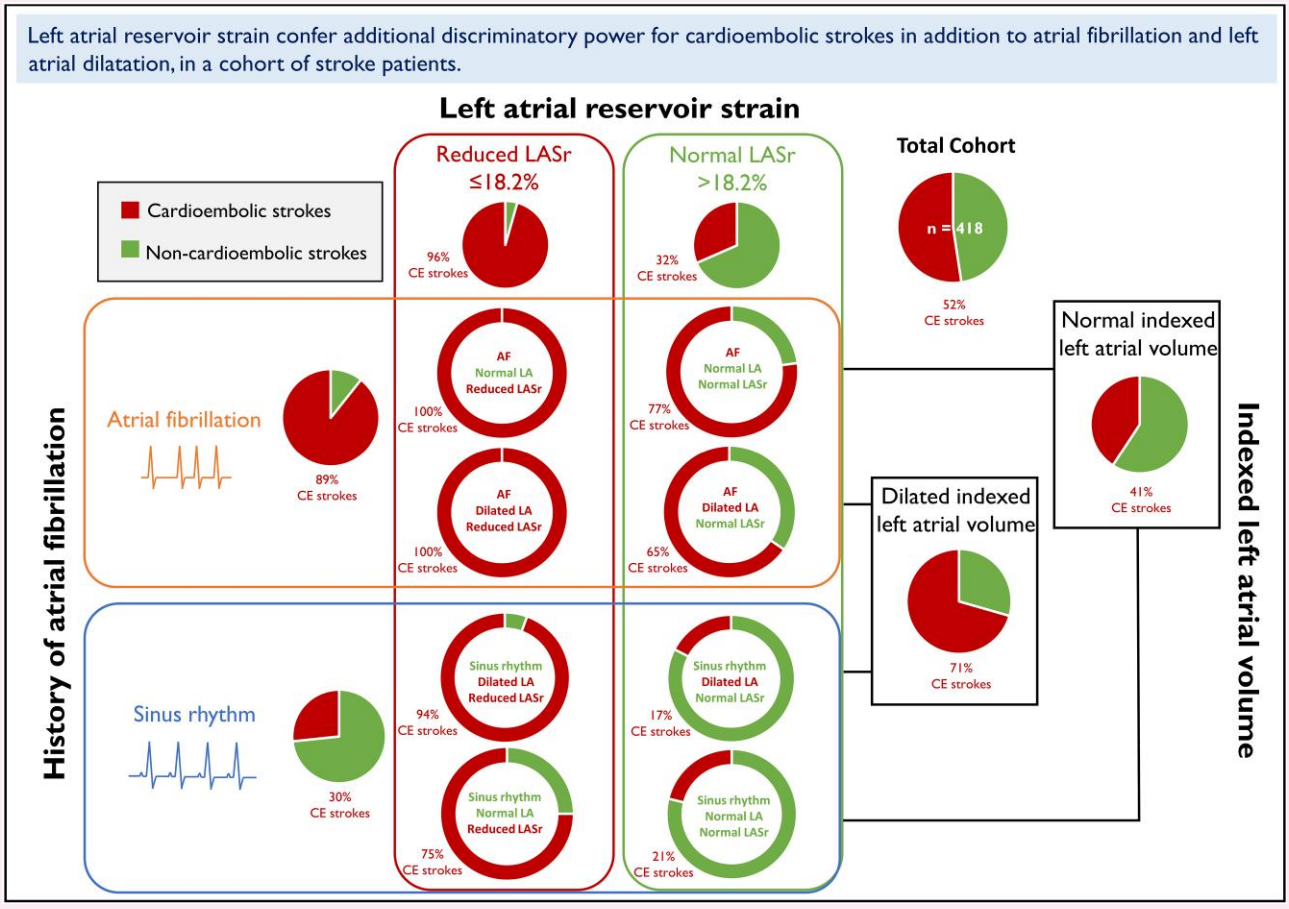
Graphical Abstract



Keywords stroke • embolism • echocardiography • heart atria • diagnosis

Introduction

Strokes caused by cardioembolism comprise a sizeable proportion of ischaemic strokes and unfortunately tend to be more debilitating with higher rates of stroke-related disability and need for institutionalized care.[1] These strokes are also associated with higher rates of stroke recurrence and mortality when compared with non-cardioembolic stroke types.[2]

The diagnostic work-up for cardioembolic aetiology in the stroke population involves assessment of the patient's clinical risk profile, rhythm status and cardiac structure and function. However, despite standardized evaluation, up to 40% of acute ischaemic strokes have no identifiable aetiology after standardized evaluation. These strokes are commonly termed 'cryptogenic' and are thought to arise from a variety of sources with a high rate of stroke recurrence.[3]

Cardiac imaging plays a pivotal role in the evaluation and work-up of patients with ischaemic stroke, with current guidelines recommending the use of echocardiography in patients with cryptogenic stroke to evaluate for cardiac sources and transcardiac pathways of cerebral embolism.[4] While traditional echocardiographic measures of left ventricular systolic and diastolic function as well as left atrial (LA) size and function have been independently associated with cardioembolic mechanisms of stroke development in the literature, contemporary studies have focused on novel measures of LA function, such as LA strain by two-dimensional speckle-tracking echocardiography, given the central role of the thrombogenic atrial substrate in the development of intracardiac thrombus formation and atrial fibrillation.[5,6] Alterations in LA strain have been demonstrated to precede changes in LA volumes and predict risk of stroke.[7] Further, our group have recently shown LA reservoir strain (LASr) to predict stroke recurrence in patients with cryptogenic stroke.[8]

Given the significant etiological heterogeneity and difficulty in identification of patients with a cardioembolic stroke mechanism, treatment in the cryptogenic stroke population can be challenging. Thus, the goal of our study was to evaluate the diagnostic performance and comparison of novel measures of LA function relative to traditional echocardiographic parameters of the left heart in patients with ischaemic stroke/transient ischaemic attack (TIA). Further, we sought to assess the use LASr in a user-defined clinical decision tree for discrimination of cardioembolic stroke subtypes when included with patient rhythm status and LA volume in this population.

Methodology

The study protocol was approved by the Western Sydney Local Health District Human Research and Ethics Committee. Informed consent was

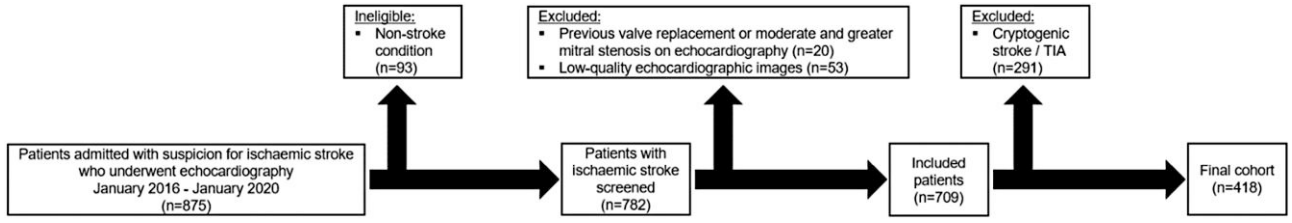


Figure 1 Study pathway. Of 875 patients screened, 418 patients met eligibility criteria and were included.

obtained from all subjects, or from the person responsible if the subject was not capable to consent to the study.

Study population and design

In this retrospective analysis of prospectively collected data, consecutive patients admitted to our institution between 1st January 2016 to 1st January 2020 with a diagnosis of ischaemic stroke or TIA who underwent transthoracic echocardiography were appraised.

The primary diagnosis of ischaemic stroke/TIA was adjudicated by the patient's treating stroke physician. Stroke classification was then performed in accordance with the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system by two independent clinicians blinded to the patient's novel echocardiographic data or the initial classification at diagnosis. We excluded patients with cryptogenic stroke, intracerebral haemorrhage, and non-stroke condition as a primary diagnosis, valvular heart disease including the presence of prosthetic heart valves or moderate and greater mitral stenosis, or those without a transthoracic echocardiogram with adequate quality images available as part of their stroke work-up (*Figure 1*).

Included patients underwent detailed clinical history and physical examination and were investigated with computed tomography and/or magnetic resonance imaging of the brain, as well as vascular imaging of the aortic arch, neck, and cerebral vessels performed with computed tomographic angiography, magnetic resonance angiography or carotid duplex sonography.

Resting electrocardiography was performed at admission and all patients underwent at least 24 h of telemetry monitoring and comprehensive transthoracic echocardiography. A subset [$n = 167$ (23.6%)] of patients underwent transesophageal echocardiography and in those with a finding of patent foramen ovale, blinded clinicians used the Risk of Paradoxical Embolism score[9] to determine the probability of causality with the index stroke event. Management strategies on discharge, in particular the use of anti-platelet agents, anticoagulants, statins, anti-hypertensives, and vasoactive medications were also recorded.

Strokes were classified in accordance with the TOAST criteria.[10] Cardioembolic strokes/TIAs were defined to include patients with arterial occlusions presumed to be due to an embolus arising in the heart. Non-cardioembolic strokes included those with strokes/TIA secondary to small vessel occlusion, large artery atherosclerosis, and strokes of other determined aetiology. Cryptogenic strokes/TIA were defined as those classified to have stroke of undetermined aetiology.

Transthoracic echocardiography

Transthoracic echocardiography was performed using commercial ultrasound systems (EPIQ, Philips Medical Systems, Andover, MA; GE-E95, GE Healthcare, Milwaukee, WI), in keeping with recommendations of the American Society of Echocardiography.[11]

LV end-diastolic and end-systolic volumes were obtained and LV ejection fraction (LVEF) was calculated by Simpson's biplane method. Normal LVEF was defined as ≥54% for women and ≥52% for men. LV mass was calculated using the Devereux formula and indexed to body surface area (BSA) to derive the indexed LV mass (LVMI). LV hypertrophy was defined as LVMI of ≥95 g/m^2 for females and ≥115 g/m^2 for males.[11]

Diastolic function was evaluated from transmitral E and A velocities, E/A ratio, average of the septal and lateral annular e' velocity, E/e', peak tricuspid regurgitant velocity, and indexed LA volume (LAVI). Diastolic grade was evaluated as per current guidelines.[12] Biplane LA volume was evaluated from apical 4- and 2-chamber views by the area-length method and indexed to BSA.[11]

Speckle-tracking echocardiography

Two-dimensional speckle-tracking strain analysis was performed offline using vendor independent software (TomTec Arena, Germany v4.6).

For LV global longitudinal strain (GLS), the LV endocardium was traced at end-systole in the three apical views. An 18-segment LV model (six segments in each apical view) was obtained and GLS was calculated as the average of the 18 segments of the left ventricle.[13]

For LA strain, the endocardium of the left atrium was manually traced at end-systole with automatic tracking throughout the cardiac cycle using R-to-R gating. The left atrium was divided into six segments (basal, mid-, and apical segments) in the apical 4- and 2-chamber views. LASr was the average of the peak systolic strain from 12 segments, LA contractile strain (LASct) the peak positive strain following the *P* wave (representative of atrial contraction) and LA conduit strain (LAScd) was the difference between the peak reservoir and contractile strain.[13]

The measurements were averaged over three cardiac cycles for patients in sinus rhythm and over five cardiac cycles for patients in atrial fibrillation.

Reproducibility analysis

Intra- and inter-observer variability was assessed by repeating LASr in 5% of the study population chosen at random from the cohort at least one month apart by the same investigator and by a second independent investigator. Reproducibility of these measurements was represented by the intra-class correlation coefficient and coefficient of variation. For LASr measurements, the interclass correlation was 0.97 (95% CI 0.95–0.98) and the coefficient of variation was 5.6% (95% CI 4.6–6.6).

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (SPSS, Inc., Chicago, Illinois) and R 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) with packages pROC and Hmisc used in the analysis for net reclassification and integrated discrimination. All tests were two-sided with a *P*-value <0.05 considered statistically significant.

Categorical variables were expressed as numbers and percentages. Continuous data were expressed as mean ± standard deviation for parameters with normal distribution or median and interquartile range for parameters that did not have a normal distribution. Differences between groups were evaluated by Student's *t*-test or its non-parametric equivalent the Mann–Whitney *U* test for continuous variables and χ^2 analyses for categorical variables.

Logistic regression was used to calculate the area under the curve (AUC) and odds ratio to predict cardioembolic stroke subtypes. AUC comparison was performed to determine the incremental diagnostic value of LASr compared with traditional echocardiographic parameters.

The incremental diagnostic value of LASr was determined by the Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) indices. These measures were obtained by fitting sequential logistic regression models using nested models. Odds ratios with their corresponding confidence intervals were calculated. The DeLong method was used to obtain confidence intervals for AUC and test the discrimination ability of the nested models.

Further, a user-defined model-based imputation decision-tree model was employed, where the variables and cut-off points were determined based on experts' practice. In the user-defined strategy, the cut-off for LAVI was defined as >34 mL/m^2 based on an established clinical cut-off value for LA dilatation.[11] In this model, the cut-off value for LASr was selected such that the predictive performance, assessed through the area under the receiver-operating characteristic (ROC) curve, was maximized. The predictive performance of the model was evaluated through the AUC from the ROC curve.

Results

Study population

Of 709 patients assessed, 418 met inclusion criteria and were classified to have either a cardioembolic ($n = 229$, mean age 72.06 ± 14.26 years, 56% male) or non-cardioembolic ($n = 189$, mean age 63.23 ± 14.72 years, 55% male) stroke/TIA. A total of 291 patients were classified as cryptogenic stroke/TIA and were excluded from the analysis. Of the included patients, 159 patients (38%) had confirmed atrial fibrillation based on electrocardiogram, cardiac rhythm monitoring or on Holter and loop recorder monitoring post discharge.

Baseline characteristics

Table 1 summarizes the baseline clinical and echocardiographic characteristics between patients with cardioembolic and non-cardioembolic strokes.

Overall, patients with cardioembolic strokes were older with a higher prevalence of ischaemic heart disease, heart failure, and atrial fibrillation ($P < 0.01$ for all). These patients also had a lower estimated glomerular filtration rate (eGFR) ($P < 0.01$), lower hemoglobin levels ($P = 0.01$) as well as lower total cholesterol and LDL-C levels ($P < 0.01$ for both). Of the modifiable cardiovascular risk factors, a higher proportion of hypertension ($P = 0.05$) and lower proportion of active smokers ($P < 0.01$) were observed amongst patients with cardioembolic strokes.

On echocardiography, patients with cardioembolic strokes were more likely to have features of LV adverse remodelling with larger LV end-systolic volumes, lower LVEF, greater LVMI, and lower LVGLS ($P < 0.01$ for all). There were higher rates of diastolic dysfunction ($P < 0.01$) amongst these patients and correspondingly, higher LV filling pressures as reflected by a higher E/e ratio ($P < 0.01$) and greater LAVI ($P < 0.01$) was present. These patients also had decreased right ventricular systolic function with lower tricuspid annual plane systolic excursion (TAPSE) and tissue Doppler-derived tricuspid lateral annular systolic velocity (S') ($P < 0.01$ for both).

LA strain

Patients with cardioembolic stroke also demonstrated reduced LA phasic function as reflected by lower LASr, LAScd and LASct respectively ($P < 0.01$ for all). To evaluate the strength of LASr in identifying cardioembolic strokes, we performed ROC curves of LASr and compared it with LVEF, LAVI, and E/e' (*Figure 2*). This showed LASr to be the most significant discriminator of cardioembolic strokes. DeLong tests showed the AUC of LASr to be significantly higher than the AUC for LVEF ($P < 0.01$), LAVI ($P < 0.01$), and E/e' ($P < 0.01$).

Decision tree analysis

We proposed a user-defined model-based imputation decision tree model based on the presence of atrial fibrillation, LA dilatation, and LASr to discriminate cardioembolic stroke subtypes. The suggested decision tree first divided patients according to the presence of comorbid atrial fibrillation, then LA dilatation (defined as LAVI >34 mL/m^2), and finally by LASr. To determine the best cut-off value of LASr, we proceeded with an empirical evaluation based on the model, where a grid of cut-off values for LASr from 12.5% to 23.5% was considered. The AUC was evaluated for each cut-off value and the cut-off value associated with the maximum AUC was selected which in this case was <18.2% (*Figure 3*).

Figure 4 demonstrates the user-defined model-based imputation decision-tree model with LASr cut off value of <18.2%. Overall, the LASr of <18.2% showed greater discrimination for cardioembolism even in patients without atrial fibrillation and normal LAVI. In patients with dilated LAVI and reduced LASr, the decision tree model showed a 100% and 94% chance of cardioembolism in those with and without atrial fibrillation, respectively. Further, in patients without comorbid atrial fibrillation and normal LAVI, the presence of reduced LASr was associated with a 75% likelihood for a cardioembolic stroke subtype.

Diagnostic value of LASr in identification of cardioembolic strokes

To determine the diagnostic value of LASr, we performed a NRI analysis which showed that the addition of LASr (cut-off <18.2%) to each conventional echocardiographic parameter improved the diagnostic performance of each model with significant improvement in the IDI indices (*Table 2*). The addition of LASr to the other echocardiographic parameters also provided significant incremental diagnostic information ($P < 0.01$ in all cases) (*Table 3*).

Clinical association of LASr

To assess the clinical value of LASr, logistic regression models based on candidate clinical and echocardiographic variables were utilized to identify significant univariable association with cardioembolic strokes; i.e. a model comprised of only clinical variables (*Table 4*) and a model combining both clinical and echocardiographic variables (*Table 5*) were examined. The inclusion of echocardiographic variables improved the predictive (likelihood ratio test $P < 0.001$) and discriminatory capacity (AUC 0.896, 95% CI 0.825–0.898, $P = 0.004$) of the model. Of the variables assessed, systolic blood pressure (OR 0.987, 95% CI 0.975–0.998, $P = 0.022$), AF (OR 16.819, 95% CI 7.688–36.793, $P < 0.001$), and LASr (OR 0.882, 95% CI 0.837–0.929, $P < 0.001$) showed significant independent associations with cardioembolic strokes.

Table 1 Baseline clinical and echocardiographic characteristics between cardioembolic and non-cardioembolic stroke groups

Variable[a]	Non-cardioembolic stroke ($n = 189$)	Cardioembolic stroke ($n = 229$)	Sig (P-value)
Demographics			
Age, years	63.0 (55–74)	74.5 (62–83)	<0.01
Male sex, *n* (%)	105 (55)	126 (56)	0.84
BMI, kg/m^2	27.6 (25–32)	26.8 (23–31)	0.23
SBP, mmHg	145.0 (125–164)	154.0 (135–175)	<0.01
DBP, mmHg	83.0 (74–93)	78.0 (69–90)	0.08
HR, bpm	75.0 (65–84)	76.0 (66–89)	0.13
Comorbidities and pharmacotherapy			
Ischaemic heart disease, *n* (%)	35 (19)	78 (34)	<0.01
Heart failure, *n* (%)	3 (2)	37 (16)	<0.01
Atrial fibrillation	12 (6)	147 (63)	<0.01
Previous stroke, *n* (%)	33 (18)	53 (23)	0.18
Hypertension, *n* (%)	128 (68)	174 (76)	0.05
Hypercholesterolemia, *n* (%)	99 (52)	115 (50)	0.70
Diabetes mellitus, *n* (%)	80 (42)	94 (41)	0.84
Peripheral vascular disease, *n* (%)	11 (6)	9 (4)	0.49
Obesity, *n* (%)	60 (32)	68 (30)	0.75
OSA, *n* (%)	6 (3)	7 (3)	1.00
Active smoking, *n* (%)	61 (32)	46 (20)	<0.01
Beta Blocker, *n* (%)	43 (23)	107 (46)	<0.01
ACEi/ARB, *n* (%)	113 (60)	93 (41)	<0.01
Dual anti-platelets, *n* (%)	73 (39)	23 (10)	<0.01
Anticoagulation, *n* (%)	15 (8)	126 (55)	<0.01
Statin, *n* (%)	163 (86)	182 (80)	0.07
Ezetimibe, *n* (%)	9 (5)	14 (6)	0.67
Serum Biochemistry			
eGFR, mL/min/1.73m^2	83 (64–90)	72 (52–87)	<0.01
Hemoglobin, g/L	138 (125–152)	134 (119–148)	0.01
Total cholesterol, mmol/L	4.50 (3.6–5.4)	3.6 (2.8–4.6)	<0.01
LDL-C, mmol/L	2.5 (1.6–3.2)	1.8 (1.2–2.6)	<0.01
HDL-C, mmol/L	1.2 (1.0–1.5)	1.2 (0.96–1.4)	0.89
Echocardiographic Parameters			
LVEDV, ml	74.9 (57–94)	75.0 (56–101)	0.15
LVESV, ml	29.1 (21–40)	32.3 (21–49)	<0.01
LVEF, %	60 (57–63)	58 (47–62)	<0.01
LVEDD, mm	42 (38–47)	45 (39–51)	0.02
LVESD, mm	27 (24–31)	30 (25–36)	<0.01
IVSD, mm	11 (9–13)	11 (9–13)	0.37
PWD, mm	10 (9–12)	10 (9–12)	0.28
LVMI, g/m^2	81 (67–102)	90 (76–116)	<0.01
LVGLS, -%	18.8 (17.0–20.8)	16.2 (12.1–19.2)	<0.01
Peak E, m/sec	0.71 (0.61–0.85)	0.82 (0.64–1.06)	<0.01
Peak A, m/sec	0.84 (0.68–1.0)	0.75 (0.56–0.94)	0.06
E/A ratio	0.82 (0.70–1.02)	0.90 (0.70–1.45)	<0.01
e' Average, cm/s	0.07 (0.06–0.08)	0.06 (0.05–0.08)	0.68
E/e' ratio	10.2 (8.1–13.4)	12.5 (9.1–17.3)	<0.01
Diastolic Grade			
Normal, *n* (%)	125 (66)	87 (38)	**<0.01**
Indeterminate, *n* (%)	23 (12)	41 (18)	0.13
Impaired, *n* (%)	41 (22)	101 (44)	<0.01

Continued

Table 1 ***Continued***

Variable[a]	Non-cardioembolic stroke ($n = 189$)	Cardioembolic stroke ($n = 229$)	Sig (P-value)
TAPSE, mm	22 (20–26)	21 (17–25)	<0.01
RVS', m/s	12.5 (10.7–14.1)	11.2 (9.3–13.1)	<0.01
LAVI, mL/m^2	25.8 (20.1–33.3)	35.2 (26.1–47.9)	<0.01
LASr, %	26.0 ± 5.5	16.7 ± 8.2	<0.01
LAScd, %	10.7 (7.7–13.5)	8.5 (6.1–11.5)	<0.01
LASct, %	14.1 ± 4.2	10.6 ± 5.4	<0.01

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CS, cryptogenic stroke; DBP, diastolic blood pressure; E/e', ratio of early diastolic mitral inflow to mitral annular tissue velocities; eGFR, estimated glomerular filtration rate; HDL-C, HDL cholesterol; HR, heart rate; IVSD, interventricular septal diameter; LDL-C, LDL cholesterol; OSA, obstructive sleep apnoea; LA, left atrial; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LASr, left atrial reservoir strain; LAEF, left atrial emptying fraction; LAVI, indexed left atrial volume; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVGLS, left ventricular global longitudinal strain; LVMI, indexed left ventricular mass; PWD , posterior wall diameter; RV, right ventricular; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion.
[a]Data are expressed as number (percentage), as the mean value ± standard deviation, or median (interquartile range-IQR).

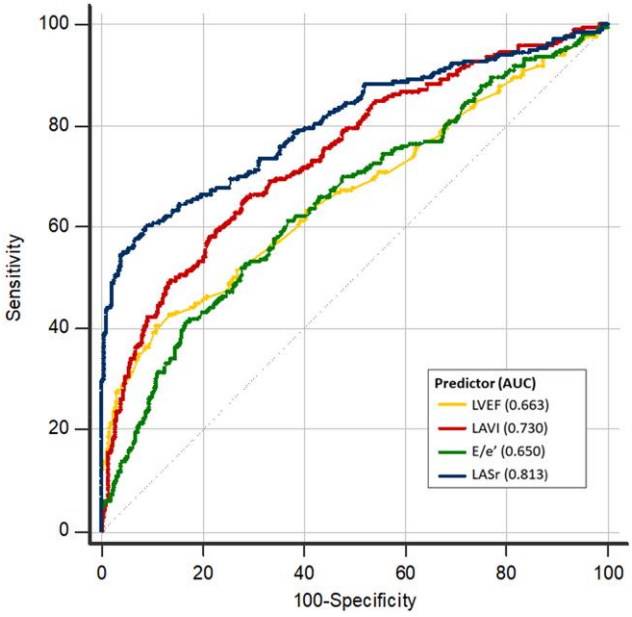


Figure 2 Receiver-operating characteristic curve. Receiver-operating characteristic curves of left heart parameters in discrimination of cardioembolic stroke subtype. Of note, left atrial reservoir strain (LASr) had the best discriminatory ability based on area under the curve and was superior to left ventricular ejection fraction (LVEF), left atrial volume index (LAVI), and E/e'.

Discussion

Cardiac imaging plays an important role in the work-up of patients with ischaemic stroke, with international guidelines suggesting use of transthoracic echocardiography as reasonable in patients with cryptogenic stroke to evaluate for cardiac sources and transcardiac pathways of cerebral embolism.[4]

Studies have identified an association between gross markers of left heart structure and function and cardioembolic stroke, with associations found with LV dysfunction as reflected through reduced LVEF[14] and LV diastolic impairment,[15] and LA pathology as reflected through increased size and reduced mechanical function.[16] In this study, we propose a clinical model-based imputation algorithm based on well-established parameters to define the probability of a cardioembolic stroke subtype. Our results show incremental diagnostic value of LASr in the discrimination of cardioembolism over conventional echocardiographic measures of left heart size and function.

Impairment of LA strain has been associated with LA fibrosis in patients with atrial fibrillation,[17] which has shown predictive value for thromboembolic events such as stroke in this population.[18,19] Of interest, in the study by Kuppahally and colleagues,[17] the relationship between LA strain and LA fibrosis was not mediated through elevation of LV filling pressures as assessed by E/e' ratio. Further, no relationship was appreciated between LV filling pressure and degree of fibrosis in

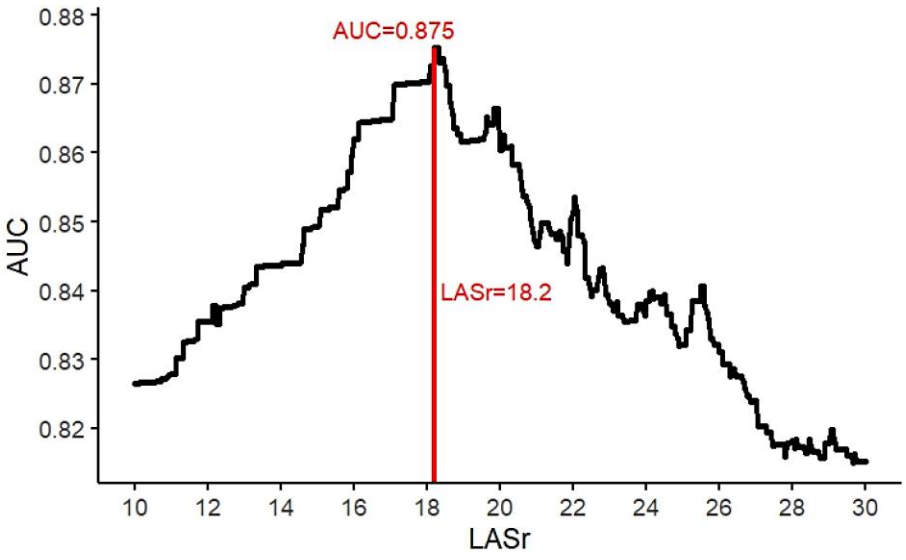


Figure 3 AUC from user-defined clinical tree. The curve highlights the AUC for a range of LASr values for the proposed clinical algorithm. A LASr of 18.2% (AUC = 0.875) in the proposed clinical algorithm, produced the best predictive performance for the clinical algorithm in detection of cardioembolic strokes. Although there were other cutoffs which presented similar AUC values, the LASr cut-off of 18.2% produced the best balance between sensitivity and specificity for the proposed clinical algorithm.

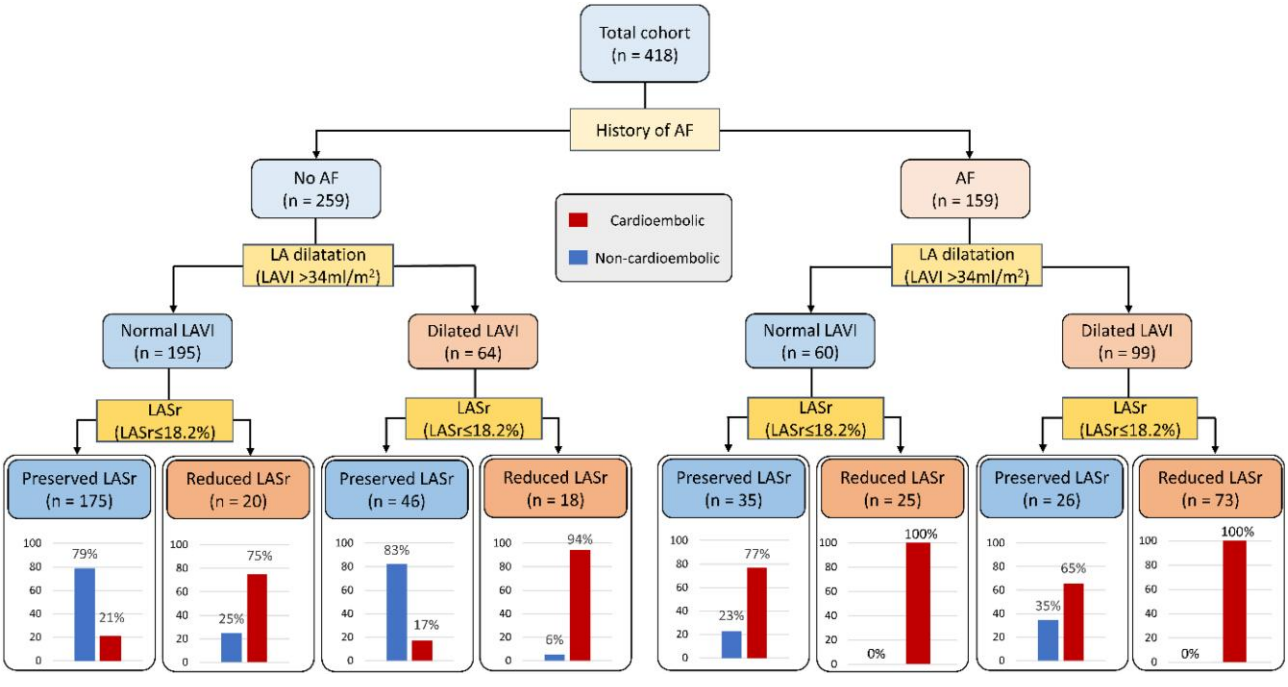


Figure 4 User-defined clinical algorithm. Proposed clinical algorithm which outlines a user-defined decision-tree model utilizing patient rhythm status, left atrial volume index (LAVI), and left atrial reservoir strain (LASr). The discriminatory performance of the proposed clinical algorithm at each decision point (node) is presented in the bar chart above. The cohort was initially stratified based on rhythm status (i.e. the presence or the absence of comorbid atrial fibrillation), following which assessment of left atrial size (i.e. LAVI) was performed based on a pre-defined cut-off for left atrial dilatation (LAVI > 34 mL/m^2). Subsequent stratification is made based on a novel measure of left atrial function (i.e. LASr); patients with LASr ≤ 18.2% were considered to have reduced LASr.

Table 2 Net reclassification improvement of adding LASr

NRI of adding left atrial reservoir strain ≤ 18.20							
	Net reclassification index (95% CI)	*P*-value	NRI for event	*P*-value	NRI for non-event	*P*-value	Integrated Discrimination Improvement (95% CI)
LVEF <50%	1.083 (0.945 to 1.220)	<0.001	0.104	0.129	0.979	<0.001	0.311 (0.267 to 0.354)
LAVI > 34 mL/m^2	1.083 (0.945 to 1.220)	<0.001	0.104	0.129	0.979	<0.001	0.267 (0.226 to 0.309)
E/e' > 15	1.083 (0.945 to 1.220)	<0.001	0.104	0.129	0.979	<0.001	0.315 (0.271 to 0.358)

Abbreviations: E/e', ratio of early diastolic mitral inflow to mitral annular tissue velocities; LAVI, left atrial volume indexed; LVEF, left ventricular ejection fraction.

Table 3 Incremental diagnostic value of LASr

Incremental diagnostic value of left atrial strain ≤ 18.20									
	Odds Ratio (95% CI)	AUC	*P*-value	AUC comparison	*P*-value	Sensitivity[a]	Specificity[a]	Sensitivity[b]	Specificity[b]
LVEF < 50%	3.985 (2.083–7.623)	0.579	<0.001	0.208 (0.171–0.244)	<0.001	22.6	93.2	55.2	98.9
LAVI > 34 mL/m^2	3.541 (2.305–5.441)	0.643	<0.001	0.142 (0.108–0.176)	<0.001	52.4	76.3	55.2	98.9
E/e' > 15	2.424 (1.527–3.850)	0.585	<0.001	0.190 (0.152–0.228)	<0.001	35.4	81.6	55.2	98.9

Abbreviations: AUC, area under the curve; E/e', ratio of early diastolic mitral inflow to mitral annular tissue velocities; LAVI, left atrial volume indexed; LVEF, left ventricular ejection fraction.
[a]Calculated from model with single predictor.
[b]Calculated from model including LASr.

Table 4 Multivariable model including clinical variables

Clinical variables	OR (95% CI)	Significance (*P*-value)
Age	1.019 (0.997–1.041)	0.089
Systolic blood pressure	0.985 (0.975–0.996)	0.005
Ischaemic heart disease	2.356 (1.235–4.497)	0.009
Heart failure	9.970 (2.407–41.296)	0.002
Atrial fibrillation	24.629 (12.088–50.180)	<0.001
Hypercholesterolemia	0.706 (0.403–1.235)	0.222
Diabetes mellitus	0.690 (0.385–1.236)	0.212
Smoking	0.923 (0.655–1.301)	0.648
Glomerular filtration rate	1.003 (0.988–1.020)	0.671

For the model including clinical variables, AUC was 0.862 (95% CI 0.825–0.898).

Table 5 Multivariable model including clinical and echocardiographic variables

Clinical variables	OR (95% CI)	Significance (*P*-value)
Age	0.999 (0.975–1.024)	0.926
Systolic blood pressure	0.987 (0.975–0.998)	0.022
Ischaemic heart disease	1.807 (0.893–3.497)	0.100
Heart failure	2.608 (0.567–11.296)	0.217
Atrial fibrillation	16.819 (7.688–36.793)	<0.001
Hypercholesterolemia	0.781 (0.423–1.442)	0.429
Diabetes mellitus	0.698 (0.370–1.317)	0.267
Smoking	0.992 (0.682–1.444)	0.967
Glomerular filtration rate	1.004 (0.987–1.022)	0.652
Left atrial volume	0.921 (0.455–1.866)	0.819
Left ventricular ejection fraction	2.161 (0.994–4.697)	0.052
E/e' ratio	1.171 (0.585–2.345)	0.656
LA reservoir strain	0.882 (0.837–0.929)	<0.001

For the combined clinical and echocardiographic variables, AUC was 0.862 (95% CI 0.825–0.898).

the study.[17] In our study, unlike LASr, measures of diastolic impairment such as E/e' ratio did not show good discrimination between cardioembolic and non-cardioembolic strokes, again suggestive of independent LA remodelling from loading conditions of the left ventricle. This finding may be secondary to atrial fibrillation and its impact on LA remodelling[20] or may represent primary pathology originating in the left atrium independent of atrial fibrillation, a disease entity frequently termed atrial cardiopathy.[21]

In our study, LAVI had incremental discriminatory capacity compared with measures of LV systolic and diastolic function, however, was inferior to LASr. The association between LA size and cerebrovascular disease has long been established in the literature, with elevations in LA dimensions and volume associated with development of incident atrial fibrillation and stroke.[22–24] More recent studies have found incremental value with addition of measures of LA function such as LASr in

prediction of atrial fibrillation in patients with cryptogenic stroke[25,26] and have identified impairments in these measures even in patients without LA dilatation.[27,28] This would suggest that early functional impairment occurs in the left atrium prior to chamber dilatation, a concept that is supported in the literature.[29,30] Of interest however, in our study we found that some patients with LA dilatation had preservation of LASr and that this combination resulted in a reduced likelihood of a cardioembolic stroke subtype. These finding suggests that there may be individual LA phenotypes present with structural and functional permutations and that these combinations may impact on degree of LA fibrosis and stroke mechanism. Further, the addition of both structural and functional changes may be additive, in particular amongst patients without comorbid atrial fibrillation.

In our study algorithm, addition of LASr to patient rhythm status and LA volume provided incremental value in discrimination of cardioembolic stroke subtypes. Similar discriminatory findings were present in both patients with sinus rhythm and atrial fibrillation, suggesting that perhaps cardioembolic stroke mechanisms may be rhythm independent and largely secondary to abnormalities in cardiac structure and function. Further, on use of net reclassification, we found significant improvement in discriminatory capacity with the addition of LASr to traditional factors associated with cardioembolic stroke mechanisms, namely reduced left ventricular systolic function, increased LA volume, and elevated E/e' ratio. This finding would suggest that addition of this novel measure in risk stratification may increase overall sensitivity and specificity for stroke mechanism determination.

Therefore, the clinical use of speckle-tracking echocardiographic-derived LASr may assist in identification of patients with a cardioembolic stroke mechanism, especially in patients without diagnosed atrial fibrillation. Further, characterization of the LA phenotype may be useful in risk stratification of patients with stroke and allow for early initiation of upstream therapies for curbing progression of adverse LA remodelling and its thrombogenic substrate as well as possible use of upfront anticoagulation in those felt to be of high risk of cardioembolism. Although our study has identified an association between LASr and cardioembolic stroke mechanisms, these findings are hypothesis generating and require further targeted studies.

Limitations

Transthoracic echocardiography represents standard practice in near all patients admitted with a diagnosis of stroke/TIA at our institution. While this represents routine care, we acknowledge that this may result in selection bias. Further, although promising, utility of LA strain imaging by speckle-tracking echocardiography has limitations. Frequently, the atrium is in the far field of imaging hence optimal image quality with adequate resolution for measurement of strain is an issue. Secondly, most currently available vendor tools for strain assessment are designed for LV strain assessment, hence achieving accurate assessment of LA strain is challenging with software discrepancies given the difference in LV and LA wall thickness.

Despite these limitations, the study has several strengths. Firstly, our study includes a large sample size extracted from a prospective ischaemic stroke database. Secondly, stroke subtype adjudication was performed by independent clinicians blinded to the patient's novel echocardiographic data providing assurance of data quality. Finally, blinding of patient information to investigators involved in measuring parameters of cardiac size and function as well as test–retest between different investigators of the same measured parameters helped ensure internal validity and reliability of the study findings.

Conclusion

LASr improves diagnostic accuracy of cardioembolic stroke beyond conventional echocardiographic measures of left heart size and function, particularly in patients without atrial fibrillation. Further studies are required to validate these findings and establish definitive cut-off values for LASr in this population.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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