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Left atrial appendage function by strain and structure is associated with thromboembolic risk in patients with cryptogenic stroke and TIA

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ABSTRACT

Background We investigated the impact of left atrial appendage (LAA) function by LAA strain, LAA morphology and subclinical atrial fibrillation (AF) on LAA thrombus presence and thromboembolic risk conditions (TRC) in patients with cryptogenic stroke and transient ischaemic attack (TIA).

Methods 185 patients (mean age 68±13 years, 33% female) were included in this prospective cohort study and underwent clinical evaluation, comprehensive transthoracic and transoesophageal echocardiography shortly after index event. LAA function and morphology were evaluated by monoplane/multiplane/speckle tracking strain and three-dimensional echocardiography. Combination of LAA thrombus and/or spontaneous echo contrast (SEC) was defined as TRC. An insertable cardiac monitor was implanted in all patients to detect subclinical AF.

Results LAA function by novel LAA strain and LAA chicken wing were independent predictors of LAA thrombus (OR 0.9 (95% CI 0.8 to 0.95), p<0.01 and OR 2.5 (95% CI 1.1 to 5.8), p=0.04, respectively). LAA chicken wing and multilobate LAA were independent predictors of TRC (OR 2.3 (95% CI 1.2 to 4.5), p=0.01 and OR 2.2 (95% CI 1.2 to 4.2), p=0.02, respectively).
LAA morphology was characterised as chicken wing in 79 (43%), windsock in 64 (34%), cactus in 35 (19%), cauliflower in 7 (4%) and multilobate LAA in 115 (62%) patients. LAA thrombus was found in 29 (16%), TRC in 123 (67%) and subclinical AF in 60 (32%) patients. Duration of subclinical AF >6 hours was associated with SEC and recurrent stroke and TIA.

Conclusion LAA function by novel LAA strain and LAA structure are independently associated with LAA thrombus and TRC in patients with cryptogenic stroke and TIA.

Trial registration number NCT02725944.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Paroxysmal atrial fibrillation (AF) is common in cryptogenic stroke and is associated with an increased risk of embolic events; however, there remains a knowledge gap regarding how left atrial—and particularly left atrial appendage (LAA)—function may relate to thromboembolic risk.

⇒ LAA is the site where most thrombi are formed in patients with clinical AF; however, prospective studies are lacking to evaluate if a specific LAA morphology is more prone to develop LAA thrombus in patients with stroke with underlying subclinical AF.

WHAT THIS STUDY ADDS

⇒ This study has demonstrated that LAA function by strain and LAA morphology were independently associated with cardiac thrombus and thromboembolic risk condition in patients with cryptogenic stroke and transient ischaemic attack, irrespectively of the detection of underlying subclinical AF during prolonged follow-up with the continuous heart rhythm monitoring.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Transoesophageal echocardiography (TOE) has, until now, primarily been recommended in younger patients following cryptogenic stroke, mainly to diagnose persistent foramen ovale.

⇒ We suggest performing TOE without an upper age limit to evaluate thromboembolic risk and to guide the most appropriate treatment and follow-up strategies.

INTRODUCTION

Cryptogenic strokes make up approximately one-third of all ischaemic strokes, and there is evidence that a large part of cryptogenic stroke and transient ischaemic attack (TIA) are of cardioembolic origin.[1 2] There is growing evidence supporting the importance of LAA function, atrial cardiomyopathy and left atrial appendage (LAA) structure in the risk stratification of patients with cryptogenic stroke.[3]

Paroxysmal atrial fibrillation (AF) is common in cryptogenic stroke.[4] Left atrial (LA) function by strain is promising to predict clinical AF in these patients.[5] However, there is a knowledge gap regarding how LA and especially LAA function may be related to thromboembolic risk. LAA function by novel

strain may be a new marker in risk prediction in patients at risk, as recently shown by our group.[6] LAA is the most prominent site for thrombus formation, and specific LAA structural features may be associated with the development of LAA thrombus in patients with stroke.[7] However, prospective randomised studies are lacking to evaluate if a specific LAA morphology is more prone to develop LAA thrombus in patients with stroke.

AF detected by 12-channel ECG[8] is an established risk factor for cardiac thrombus, spontaneous echo contrast (SEC) and cerebral embolism.[9] Approximately one-third of patients with cryptogenic stroke have episodes with subclinical AF, defined as short episodes of paroxysmal AF detected during long-time follow-up by insertable cardiac monitor (ICM),[4 10] and these patients may be at high risk for recurrent stroke.[11] Whether subclinical AF is a risk factor or merely a marker of risk remains controversial. LA, in particular, LAA thrombi are mainly—but not exclusively—observed in patients with clinical AF.[12] Moreover, no temporal relationship has been found between subclinical, device-detected AF and thromboembolic complications.[13]

The present study aimed to investigate the impact of LAA function by strain, LAA structure and subclinical AF on LAA thrombus and thromboembolic risk in patients with cryptogenic stroke and TIA.

PATIENTS AND METHODS

Study design and population

Patients with cryptogenic stroke or TIA from the Department of Neurology were referred to the Department of Cardiology Akershus University Hospital from May 2016 until June 2018 and included in the single-centre, prospective PROACTIA study (online supplemental file 1).[14] Patients aged >18 years were screened by two neurologists and a cardiologist. Patients with ischaemic stroke, classified as cryptogenic according to the TOAST criteria[15] (non-lacunar stroke or suspected cortical TIA; absence of ipsilateral intracranial/extracranial stenosis; no major risk factors for cardiac embolism and no other specific cause of stroke, such as known or newly detected clinical AF lasting >30 s),[1] were screened for eligibility. Eligible patients with complete transthoracic (TTE) and transoesophageal echocardiographic (TEE) examinations (Vivid E9 and E95, GE Vingmed, Horten, Norway) were included. The trial is registered at ClinicalTrials.gov ((identifier: NCT02725944).

Clinical examination and detection of subclinical AF

All study patients were screened for clinical AF lasting >30 s using a 12-lead resting ECG, following the guidelines.[8] Paroxysmal clinical AF was also assessed prior to inclusion using a 24-hour Holter ECG recorded by the OxyHolter Recorder (Maynard, Massachusetts, USA). Only patients without detected clinical paroxysmal AF were included. ICMs (Reveal Linq; Medtronic, Minneapolis, MN, USA) were implanted in all included patients to detect subclinical AF, defined as episodes of irregular heart rhythm with variable RR interval and absent P waves, lasting >30 s.[8] Secondary stroke prevention was initiated with antiplatelet therapy or oral anticoagulation in all patients depending on detection of subclinical AF. Home monitoring analyses were performed once weekly during the follow-up.

CT and MRI

All study patients underwent neurovascular imaging by CT, MRI or both to verify a non-lacunar ischaemic stroke.[14]

Transthoracic and transoesophageal echocardiography

All patients underwent TTE and two-dimensional (2D) and three-dimensional (3D) TEE after index cerebral event (median 4 days (IQR 3–6 days)). LA/LAA views by TEE with mid-range gain settings, a narrow image sector (to increase frame rate to 40–60 frames/s), zoomed and wide-angle gated acquisition of multiple volumes were achieved at mid-oesophageal TEE views with imaging axis at 0–180 degrees of three consecutive, regular beats. Prior to study inclusion, the patients were screened by conventional 2D TTE and TEE imaging analyses of left ventricle (LV), LA and LAA morphology and function, according to current recommendations.[16–18]

The echocardiographic datasets were retrospectively analysed off-line (EchoPac software V.203, GE Healthcare, Horten, Norway and ComPACS, V.10.6, MediMatic, Genova, Italy) by three operators (JS, LS-S and EBO), blinded to clinical data. The 2D monoplane/multiplane and 3D TEE imaging analyses were performed to further classify LAA type (figure 1a), LAA SEC and thrombus (figure 1b) and LA/LAA function by strain speckle-tracking analyses (figure 2a,b). The largest dimensions and best imaging qualities of the LAA (depth and diameter) were acquired, preferably at imaging axis planes of 45–135 degrees.[18] LA/LAA SEC was defined as smoke-like or swirl echoes, visualised on echocardiography. Thrombus appears as an echo-dense, solid mass in LA/LAA/LV[19] (figure 1b). Thromboembolic risk conditions were defined as a combination of thrombus and/or SEC.

Comprehensive assessment of persistent foramen ovale (PFO) by TEE included measurement of maximal size at its right atrial and LA ends, as well as evaluation for any additional defects from the mid-oesophageal inflow-outflow view at 0–180 degrees. Colour Doppler and agitated saline contrast studies, both with and without physiological Valsalva manoeuvre, were performed at 90–120 degrees. Furthermore, 3D TEE imaging was performed to improve visualisation of the PFO, allowing multiple acquisition modes, including narrow-angle, zoomed and wide-angle gated acquisition of multiple volumes.[18]

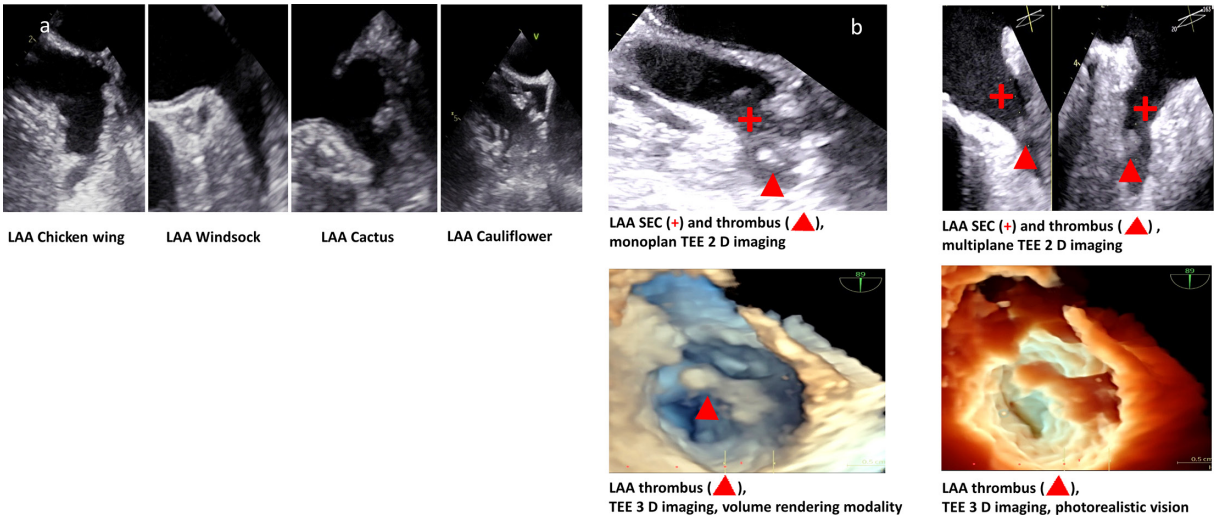

Figure 1 (a) Four different LAA types as shown by TEE from study patients. (b) LAA showing SEC and thrombus by 2D TEE (upper row) and 3D TEE (lower row) in study patients. 2D, two-dimensional; 3D, three-dimensional; LAA, left atrial appendage; SEC, spontaneous echo contrast; TEE, transoesophageal echocardiography.

Left atrial and left atrial appendage speckle tracking strain echocardiography

Triphasic LA strain—comprising LA reservoir strain (LA-Sr), LA conduit strain (LA-Scd) and LA contraction strain (LA-Sct)—was assessed using an LA-focused four-chamber view, following EAVCI recommendations.[20 21] The resulting LA strain curves provided two peaks corresponding to LA-Sr and LA-Sct, with the difference between these peaks representing LA-Scd.

TEE evaluation of LAA function by speckle tracking strain analysis was performed; however, specific software for evaluating LAA strain by speckle tracking is not yet available. Therefore, we analysed LAA strain by EchoPac software, developed for the LV four-chamber view. All four LAA types were found to have a dominant lobe (figure 1). Thus, we performed our measurements on the main lobe by standardised acquisition of the whole length of the main LAA lobe in the long axis view. A six-segment LAA strain model was established (figure 2a,b) by standardised acquisition of the whole length of the LAA (long axis view), bearing in mind the morphologic variability of the LAA.

The onset of the QRS complex was used as a reference point (figure 2a,b). Endocardial LAA border was traced

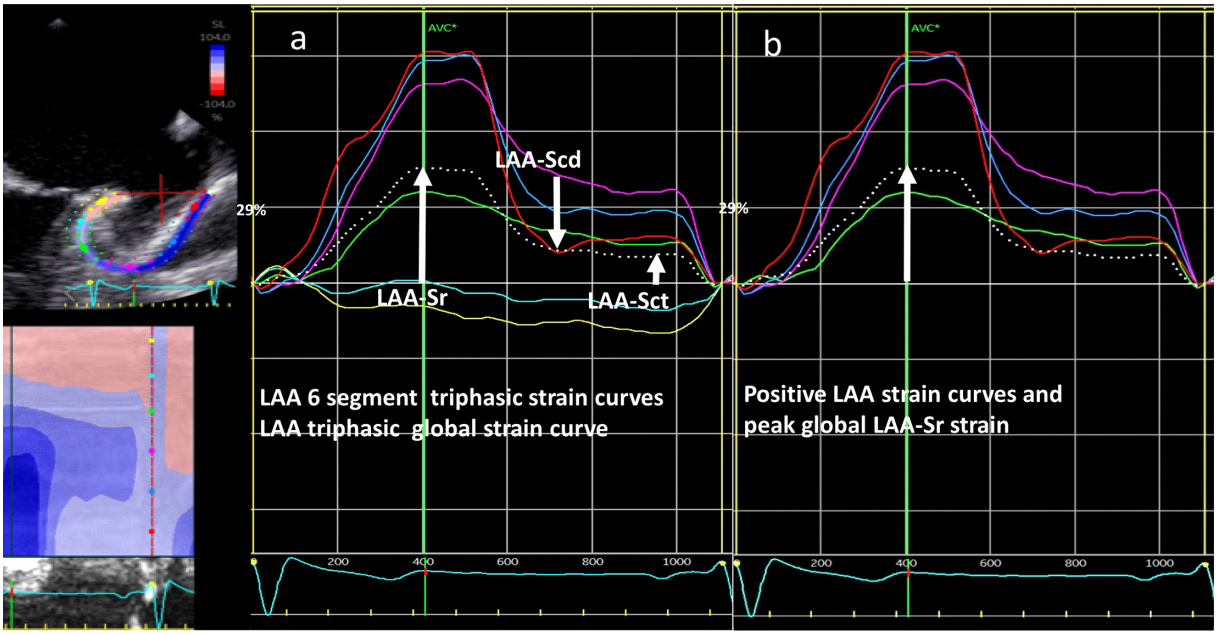

Figure 2 (a, b) LAA function by strain imaging. (a) All six LAA triphasic strain curves (positive and negative) and LAA global strain curve (white); vertical white arrows indicate the amplitudes of global LAA-Sr, LAA-Scd and LAA-Sct. (b) LAA-positive triphasic strain curves, vertical white arrow indicates peak global LAA-Sr strain. LAA-Scd, left atrial appendage conduit strain; LAA-Sct, left atrial appendage contraction strain; LAA-Sr, left atrial appendage reservoir strain.

manually by a point and click technique. The region of interest was adjusted to a default width of 3 mm, considering the thin wall of the LAA, and the imaging software automatically identified six LAA segments. Segmental and global LAA strain curves were then generated. All strain analyses were performed offline from digitally stored cine loops, with manual adjustment of region of interest when necessary to optimise speckle tracking. The resulting LAA strain curves were triphasic and characterised by three measurements, similar to LA strain: two peaks corresponding to LAA reservoir strain (LAA-Sr) and LAA-contraction strain (LAA-Sct), respectively. The difference between these was defined as LAA conduction strain (LAA-Scd). LAA strain analysis included peak positive LAA-Sr strain, peak negative LAA-Scd and peak negative LAA-Sct strain, which were generated, measured and reported. Strain curves from all six LAA segments were averaged as global LAA-Sr strain (figure 2a,b). Only LAA strain curves with >75% positive concordance were included (according to the GE imaging software strain algorithm) to overcome LAA strain measurement failure caused by LV myocardial deformation pattern close to LAA (figure 2a).

Statistical analysis

Data were presented as mean±SD or as median with IQR. Categorical variables were compared using the χ^2 test or Fisher's exact test and continuous variables were compared using the unpaired Student's t-test, analysis of variance or Kruskal-Wallis test, as appropriate. Statistical analyses were performed using SPSS V.26.0 (Chicago, Illinois, USA). Univariable and multivariable logistic regression analyses were performed to assess predictors of LAA thrombus and thromboembolic risk condition. C-statistics were calculated by receiver operating characteristic (ROC) curves to assess the parameters' ability to predict thrombus formation. Multicollinearity was defined by correlation coefficients >0.7. Interobserver and intraobserver variability was expressed by intraclass correlation coefficients. Two-sided p values <0.05 were considered statistically significant.

RESULTS

Demographics and clinical characteristics

185 patients (mean age 68±13 years, 33% female) with cryptogenic stroke or TIA and TTE and TEE imaging were included with a median follow-up with continuous ICM monitoring for 849 days (IQR 663–1045 days). Clinical and echocardiographic characteristics of 185 study patients are shown in table 1. Participants had a high burden of comorbidity with a median CHA2DS2-VASc score of 4.2 (±1.4). CHA2DS2-VASc score was not different in patients with thrombus or thromboembolic risk condition compared with those without (table 2). Qualifying event was cryptogenic stroke in 133 (72%) patients and TIA in 52 (28%) patients. No significant differences were found in the frequency of thrombus and thromboembolic risk condition, subclinical AF or LAA function by strain in patients with stroke compared with those with TIA (table 2). Twenty-four (13%) of the patients were treated with thrombolysis. There were no differences in frequency of thrombus, thromboembolic risk condition, subclinical AF or LAA function by strain in patients with thrombolysis compared with those without (table 2).

Recurrent stroke or TIA occurred in 14 patients (7.6 %), and death occurred in three (1.6%) patients during follow-up. The median follow-up duration was 396 days (IQR 152–649 days) for recurrent stroke or TIA and 589 days (IQR 426–722) days for death after index event. Neither thromboembolic risk condition nor LAA thrombus was associated with recurrent stroke or TIA (table 2). Sixty patients (32.4%) developed subclinical AF (median 149 days, IQR 33–379 days). Cumulative

Table 1 Baseline clinical, arrhythmic and echocardiographic characteristics in 185 study patients with cryptogenic stroke/TIA

Age at diagnosis (years)	68±13
Female gender (n/%)	61/33
Body mass index (kg/m^2)	27.7±4.3
Heart rate (bpm)	65±11
Cryptogenic stroke (n/%)	133/72
Cryptogenic TIA (n/%)	52/28
CHA2DS2-VASc score (n)	4.2±1.4
Hypertension (n/%)	113/61
Heart failure (n/%)	7/4
Diabetes mellitus (n/%)	11/22
Smoking, including previous (n/%)	75/41
Current smoking (n/%)	20/11
Recurrent stroke/TIA (n/%)	14/8
Death (n/%)	3/2
Subclinical AF (n/%)	60/32
Echocardiography in SR (n/%)	185/100
LAA thrombus (n/%)	29/16
LAA SEC (n/%)	121/65
TRC (n/%)	123/67
LAA type CW (n/%)	79/43
LAA type WS (n/%)	64/35
LAA type cactus (n/%)	35/19
LAA type CF (n/%)	7/4
LAA >1 lobe (n/%)	115/62
PFO (n/%)	102/55

AF, atrial fibrillation; LAA, left atrial appendage; LAA CF, left atrial appendage type cauliflower; LAA CW, left atrial appendage type chicken wing; PFO, persistent foramen ovale; SEC, spontaneous echo contrast; SR, sinus rhythm; TIA, transient ischaemic attack; TRC, thromboembolic risk condition; LAA WS, left atrial appendage type windsock.

Table 2 Clinical, transthoracic and transoesophageal echocardiographic characteristics in 185 patients with cryptogenic stroke/TIA divided in three groups: SR versus subclinical AF, no LAA TRC versus LAA TRC and no LAA thrombus versus LAA thrombus

	SR, 125/68%	Subclinical AF, 60/32%	P value	No LAA-TRC, 62/33%	LAA-TRC, 123/67%	P value	No LAA-thrombus, 156/84%	LAA-thrombus, 29/16%	P value
Clinical characteristics									
Age, years	67±13	71±11	0.02	68±13	68±13	0.91	68±13	68±9	0.88
Female (n/%)	43/34	18/30	0.55	19/31	42/34	0.63	54/35	7/24	0.27
Hypertension (0/1) (n/%)	69/55	44/73	0.02	40/65	73/59	0.50	97/62	16/55	0.48
Systolic BP (mm Hg)	140±20	146±19	0.03	142±22	141±19	0.67	141±20	143±17	0.66
Diastolic BP (mm Hg)	77±11	78±10	0.54	77±11	78±11	0.45	77±10	82±12	0.01
CHA2DS2-VASc score, n (IQR)	4.0±1.4	4.5±1.3	0.05	4.1±1.4	4.2±1.4	0.88	4.2±1.4	4.2±1.5	0.86
CHA2DS2-VASc score, quartiles, n (IQR)	2.1±1.2	2.5±1.1	<0.05	2.3±1.1	2.2±1.2	0.79	2.3±1.1	2.2±1.2	0.84
Troponin T, ng/L (IQR)	10±8	13±15	0.11	10±7	12±9	0.15	11/10	13/8	0.12
NT-proBNP, ng/L (IQR)	92±227	203±55	0.02	93±27	152±310	0.16	123±291	127±255	0.29
Subclinical AF (n/%)	NA	NA	NA	19/31	41/68	0.71	54/35	6/21	0.14
Subclinical AF >6 hours (n/%)	NA	NA	NA	7/11	21/17	0.30	26/17	2/7	0.26
Stroke/TIA (1/0) (n/%)	87/70	46/77	0.32	44/71	89/72	0.84	111/71	22/76	0.61
Thrombolysis (1/0) (n/%)	13/10	11/18	0.13	6/10	18/15	0.34	19/12	5/17	0.55
Recurrent stroke/TIA (n/%)	7/6	7/12	0.12	5/8	9/7	1.00	12/8	2/7	1.00
Transthoracic echocardiography									
LV end-diastolic diameter (mm)	52±7	55±7	0.02	53±6	53±7	0.61	53±6	55±7	0.15
LV mass index (g/m^2)	94±28	103±26	0.03	94±23	99±25	0.63	96±25	105±24	0.04
LVEF (%)	63±8	63±8	0.97	64±8	63±7	0.37	64±7	60±8	<0.01
E/e'	12±5	14±5	0.12	12±5	13±5	0.10	13±5	12±5	0.92
LAVI (mL/m^2)	35±9	42±11	<0.001	38±10	37±10	0.38	37±10	37±9	0.87
LA-Sr (%)	27±7	28±8	0.68	28±6	27±8	0.64	30±7	26±8	0.16
Transoesophageal echocardiography									
LAA emptying velocity (cm/s)	80±21	81±23	0.71	81±20	80±23	0.82	81±23	78±17	0.40
LAA filling velocity (cm/s)	60±13	59±14	0.56	62±15	58±12	0.049	60±14	58±11	0.56
LAA thrombus (n/%)	23/18	6/10	0.14	0/0	29/100	<0.001	NA	NA	NA
LAA-TRC (n/%)	82/66	41/68	0.71	NA	NA	NA	94/60	29/100	<0.001
PFO (n/%)	69/55	33/55	0.98	39/63	63/51	0.13	88/56	14/48	0.42
LAA type chicken wing (n/%)	54/43	25/42	0.84	18/29	61/50	< 0.01	62/40	17/59	0.06
LAA type windsock (n/%)	43/34	21/35	0.94	24/39	40/33	0.40	56/36	8/28	0.39

Continued

Table 2 Continued

	SR, 125/68%	Subclinical AF, 60/32%	P value	No LAA-TRC, 62/33%	LAA-TRC, 123/67%	P value	No LAA-thrombus, 156/84%	LAA-thrombus, 29/16%	P value
LAA type cactus (n/%)	24/19	11/18	0.89	16/26	19/15	0.09	33/21	2/7	0.07
LAA type cauliflower (n/%)	4/3	3/5	0.68	4/7	3/2	0.23	5/3	2/7	0.30
LAA multilobate (n/%)	79/63	36/60	0.67	32/52	83/68	0.04	95/61	20/69	0.41
LAA-Sr (%)	25.5±6.5	19.2±4.6	<0.001	24.6±6.7	23.0±6.5	0.14	24.2±6.7	20.1±4.8	<0.01

Values are mean±SD. P values are calculated using analysis of variance or the Kruskal-Wallis test, and the χ^2 test or Fisher's exact test, as appropriate.
AF, atrial fibrillation; BP, blood pressure; LAA, left atrial appendage; LAA-Sr, left atrial appendage reservoir strain; LA-Sr, left atrial reservoir strain; LAVI, left atrial systolic volume index; LV, left ventricle; LVEF, left ventricle ejection fraction; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PFO, persistent foramen ovale; SR, sinus rhythm; TIA, transient ischaemic attack; TRC, thromboembolic risk condition.

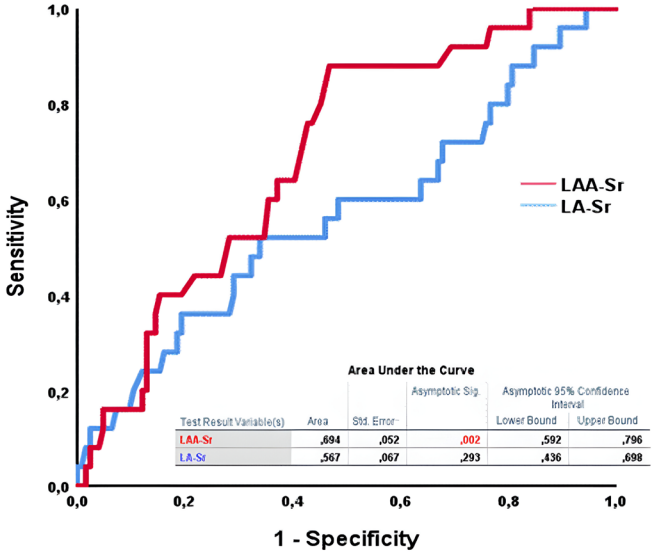

Figure 3 ROC analyses of LAA strain and LA strain to predict LAA thrombus. By ROC analyses, an LAA-Sr cut-off value of 23.2% detected LAA thrombus significantly and independently with an area under the curve (AUC) of 0.69 with a sensitivity of 88% and a specificity of 53%. LAA-Sr, left atrial appendage reservoir strain; LA-Sr, left atrial reservoir strain; ROC, receiver operating characteristic.

subclinical AF burden was <6 min in 12 (7%) patients, >6 min and <6 hours in 20 (11%) patients and >6 hours in 28 (15%) patients. In patients with the highest burden of subclinical AF (>6 hours), we found a significant association with recurrent stroke or TIA and LAA SEC by univariable analyses with an OR 5.1 (95% CI 1.6 to 16.0, p<0.01) and OR 2.9 (95% CI 1.3 to 6.7, p=0.01).

TTE and TEE imaging

Results from TTE and TEE imaging are presented in table 2.

LAA function by strain showed a strong correlation between LAA-Sr and LAA-Scd (R=0.80, p<0.001) and LAA-Sr and LAA-Sct (R=0.77, p<0.001). Hence, we defined the LAA function by LAA-Sr as LAA strain. Similarly, LA function was defined by LA-Sr as LA strain.

LAA strain was significantly impaired in patients with LAA thrombus and those with subclinical AF, while LA strain was not (table 2). By ROC analyses, LAA strain detected LAA thrombus independently with a cut-off value of 23.2% and an area under the curve of 0.69 with a sensitivity of 88% and a specificity of 53%, while LA did not (figure 3). LAA velocities were reduced in study patients with thromboembolic risk conditions compared with those without, but not in patients with LAA thrombus (table 2). Furthermore, LAA strain was impaired in patients with recurrent stroke compared with those without (LAA-Sr 19.8±3.3% vs 23.8±6.7%, p=0.03).

Significant markers of LAA thrombus, thromboembolic risk condition and subclinical AF by univariable logistic regression analyses are shown in table 3. By multivariable analyses, LAA strain and LAA chicken wing were independent predictors of LAA thrombus, OR 0.9 (95%

Table 3 Univariable logistic regression analyses with significant predictors for LAA TRC, LAA thrombus and subclinical AF in 185 patients with cryptogenic stroke/TIA

	OR	95% CI	P value
LAA TRC			
LAA CW	2.41	1.25 to 4.62	<0.01
LAA multilobate	1.95	1.04 to 3.63	<0.05
LAA thrombus			
LV mass index (g/m^2)	1.01	1.00 to 1.03	<0.05
LVEF (%)	0.92	0.88 to 0.97	<0.01
LAA-Sr (%)	0.89	0.82 to 0.96	<0.01
LAA SEC 1/0	18.97	2.52 to 143.00	<0.01
Subclinical AF			
Hypertension, 1/0	2.23	1.14 to 4.37	<0.05
CHA2DS2-VASc by quartiles	1.32	1.00 to 1.73	<0.05
LAVI (mL/m^2)	1.07	1.04 to 1.11	<0.001
LV end-diastolic diameter (mm)	1.06	1.01 to 1.11	<0.05
LV mass index (g/m^2)	1.01	1.00 to 1.02	<0.05
LAA neck diameter (mm)	1.14	1.04 to 1.26	<0.01
LAA EDV 2D (mL)	2.06	1.29 to 3.28	<0.01
LAA ESV 2D (mL)	1.19	1.03 to 1.38	<0.05
LAA-Sr (%)	0.80	0.74 to 0.87	<0.001

AF, atrial fibrillation; 2D, two-dimensional; EDV, end diastolic volume; ESV, end systolic volume; LAA, left atrial appendage; LAA CW, left atrial appendage type cauliflower; LAA-Sr, left atrial appendage reservoir strain; LAVI, left atrial volume index; LV, left ventricle; LVEF, left ventricle ejection fraction; SEC, spontaneous echo contrast; TIA, transient ischaemic attack; TRC, thromboembolic risk condition.

Table 4 Multivariable logistic regression analyses of clinical and transoesophageal echocardiographic parameters to predict the risk for LAA TRC and LAA thrombus, adjusted for CHA2DS2-VASc

	OR	95% CI	P value
LAA TRC			
Model 1			
CHA2DS2-VASc (n)	0.98	0.79 to 1.22	0.86
LAA CW	2.32	1.19 to 4.51	0.01
LAA-Sr (%)	0.96	0.92 to 1.01	0.12
LAA TRC			
Model 2			
CHA2DS2-VASc (n)	1	0.80 to 1.25	1
LAA multilobate	2.2	1.16 to 4.17	0.02
LAA-Sr (%)	0.96	0.92 to 1.01	0.14
LAA thrombus			
Model 3			
CHA2DS2-VASc (n)	0.82	0.60 to 1.12	0.22
LAA CW	2.49	1.06 to 5.83	0.04
LAA-Sr (%)	0.87	0.80 to 0.95	<0.01
LAA thrombus			
Model 4			
CHA2DS2-VASc (n)	0.85	0.63 to 1.15	0.3
LAA multilobate	1.54	0.64 to 3.73	0.34
LAA-Sr (%)	0.88	0.81 to 0.95	<0.01

LAA, left atrial appendage; LAA CW, left atrial appendage type chicken wing; LAA-Sr, left atrial appendage reservoir strain; TRC, thromboembolic risk condition.

CI 0.8 to 0.95), p<0.01 and OR 2.5 (95% CI 1.1 to 5.8), p=0.04, respectively (table 4). Furthermore, LAA chicken wing and multilobate LAA were independent predictors of thromboembolic risk condition (OR 2.3 (95% CI 1.2 to 4.5), p=0.01 and OR 2.2 (95% CI 1.2 to 4.2), p=0.02, respectively (table 4). Additionally, LAA SEC was highly prevalent in study patients and was significantly associated with LAA thrombus compared with those without, 97% vs 60%, p<0.001 (table 2).

The frequency of PFO was increased in study patients (102/55%) compared with the general population.[22] PFO frequency in patients aged <60 years (45/24%) was 26 (58%) compared with 76 (54%) (p=0.68) in patients aged >60 years (140/76%). PFO was not associated with thromboembolic risk condition, thrombus (table 2) or recurrent stroke (p=0.34) in the study population.

Intraobserver and interobserver intraclass correlation for LAA-Sr, LAA-type, thromboembolic risk condition and LAA thrombus in 10 random patients were 0.99 (95% CI 0.97 to 0.99) and 0.91 (95% CI 0.63 to 0.98); 1.00 (95% CI 1.00 to 1.00) and 0.88 (95% CI 0.40 to 0.98); 1.00 (95% CI 1.00 to 1.00) and 0.85 (95% CI 0.26 to 0.97); 1.00 (95% CI 1.00 to 1.00) and 0.87 (95% CI 0.36 to 0.98), respectively.

DISCUSSION

The present study has demonstrated LAA strain as a novel method to measure LAA function and an independent marker of LAA thrombus in patients at risk. LAA strain and LAA chicken wing were independently associated with LAA thrombus, while LAA chicken wing and multilobate LAA were independently associated with thromboembolic risk condition. Neither LAA thromboembolic risk condition nor LAA thrombus was associated with recurrence of stroke or TIA. Only patients with the highest burden of subclinical AF (>6 hours) were at significantly increased risk of recurrent stroke or TIA and LAA SEC.

Our results emphasise the ability of LAA strain as a new surrogate for LAA function and a marker of thrombosis in patients with cryptogenic stroke/TIA. LAA strain was reduced in patients with recurrent stroke and served as a marker of subclinical AF, as shown by our group.[6] Specific types of LAA morphologies were associated with thrombus and thromboembolic risk condition in this

patient group, and thromboembolic risk condition was highly associated with thrombosis.

Our study has demonstrated that the development of thromboembolic risk conditions and LAA thrombus is a complex mechanism, involving several factors, including LAA function and morphology, highlighting the importance of atrial cardiomyopathy in the diagnostic workup of these patients. Atrial cardiomyopathy may be a determinant of arrhythmia progression[23] and a bystander in the complex interplay to facilitate prothrombotic stages, thrombus and cardioembolic stroke.[12 24] Further studies, however, are needed to investigate these interactions in patients at risk.

The concept of atrial cardiomyopathy has been defined as any complex structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations.[25] These manifestations include impaired LA/LAA function, atrial fibrosis, inflammation, prothrombotic stages, AF and stroke and may explain the lack of temporal relationship between AF, thrombogenesis and stroke.[12] In the present study, we demonstrated that LAA function by strain was significantly reduced both in patients with thrombus, SEC, recurrent stroke and subclinical AF. LAA strain was an independent marker of LAA thrombus, which may indicate that impaired LAA function is a more important risk factor of thrombus in LAA than subclinical AF. Thus, subclinical AF may rather be a marker of risk than a risk factor for thrombus.

Clinical AF is an established risk factor for stroke, and impaired LA function by strain has been shown to predict clinical AF in patients at risk in several studies and is associated with increased risk of cardiac embolism.[9 26] Moreover, impaired LA function by strain is a marker of atrial fibrosis, which is associated with LAA thrombus, SEC and stroke in patients with clinical AF.[27] Our results expand the complex interaction between impaired atrial function (including impaired LAA function), thrombogenesis, clinical and subclinical AF and stroke.[9 26]

Thrombus was not associated with recurrent stroke/TIA in this selected study population. However, in patients with the highest burden of subclinical AF (>6 hours), we found a significant association with both recurrent stroke/TIA and LAA SEC. The frequency of recurrent stroke/TIA was low (14/7.6%), and only 2/29 (7%) occurred in patients with LAA thrombus compared with 12/156 (8%) without LAA thrombus (ns). The best clinical practice for patients with cryptogenic stroke/TIA may be to perform comprehensive TTE and TEE examination shortly after hospital admission to investigate potential cardioembolic sources. The present study demonstrated that multimodality and novel echocardiography imaging modes may increase the accuracy and yield to diagnose cardioembolic sources in patients with cryptogenic stroke/TIA. Whether the present TEE imaging approach may improve treatment in patients at risk should be evaluated in randomised studies.

The frequency of PFO was increased in study patients compared with the general population.[22 28] However, the frequency of PFO was not increased in patients aged <60 years compared with patients aged >60 years. Additionally, PFO was not associated with thromboembolic risk conditions, thrombus (table 2) or recurrent stroke, which aligns with findings from recent studies.[3 29] The pathogenic role of PFO in patients with stroke has been discussed for decades; most cryptogenic strokes are embolic, and embolisms can originate from multiple minor-risk cardiogenic sources and supracardiac atherosclerosis.

Limitations of the study

Patients with cryptogenic stroke/TIA were included without a matched and age-adjusted control group to compare the prevalence of subclinical AF, SEC, sludge and thrombus in LAA. To perform a TEE examination in a normal population with the potential risk of adverse events is not considered as good ethical practice and would not have been accepted by the regional ethics committee in Norway. Cardiac CT and MRI may improve the accuracy of the LAA thrombus diagnosis and further studies may investigate this multimodality approach. Normal LAA strain values are not reported in the literature yet, and therefore, we could only present values in patients with cryptogenic stroke/TIA. Variability in strain is vendor dependent, and there is no specific software for evaluating LAA strain. We used only one echocardiographic vendor in this study. At last, LAA strain may vary because of different LAA morphologies.

CONCLUSIONS

LLA function, assessed by novel strain and morphology measures, was independently associated with cardiac thrombus and thromboembolic risk condition in patients with cryptogenic stroke and TIA.

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