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Evidence of subtle left ventricular systolic dysfunction in cryptogenic stroke in the young

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Abstract

Introduction: Ischemic stroke in young patients often remains cryptogenic, that is, no underlying reason can be found. Some of these strokes may originate in the heart. Left ventricular (LV) dynamic volumetry and strain analysis are relatively new and promising methods for evaluating LV function.

Methods: In this pilot study, we recruited 30 young (18-50 years) patients with cryptogenic ischemic stroke and 30 age- and sex-matched controls from the SECRETO study (NCT01934725). The LV systolic function was assessed by LV volumetry (ejection fraction, peak emptying rate, and time to peak emptying rate). The longitudinal systolic function was assessed by speckle tracking strain and strain rate imaging, and by tissue velocity imaging derived MAD (mitral annular displacement) and septal S'.

Results: Stroke patients had less vigorous global longitudinal strain (median −18.9, interquartile range 3.3), compared to healthy controls (median −20.0, interquartile range 2.8), $P = .010$. There was no statistically significant differences in septal S', MAD, global longitudinal strain rate, or dynamic volumetry-derived parameters between the two groups.

Conclusions: Young cryptogenic stroke patients have subtly altered systolic function compared to healthy controls, found merely with longitudinal strain analysis. This infers that the heart may play a role in the pathogenesis of cryptogenic ischemic stroke.

KEYWORDS
echocardiography, ischemic stroke, strain, strain rate imaging, three-dimensional echocardiography

1 | INTRODUCTION

Cryptogenic stroke constitutes a group of stroke patients in whom stroke mechanisms remain elusive after complete diagnostic work-up. Cryptogenic strokes are especially frequent among young stroke patients, in whom stroke is particularly devastating, since these patients have a career and parenting life ahead of them, and suffering a stroke often affects these domains in a negative way.[1]

Part of cryptogenic strokes represents cardiogenic embolization. One of the recognized mechanisms of cryptogenic stroke is

paradoxical embolism. This is likely particularly in patients with a large patent foramen ovale (PFO) or atrial septal aneurysm associated with PFO, although it remains a challenge to determine the causality of PFO at individual level.[2] Furthermore, in the remaining patients' neuroimaging frequently also suggests an embolic pattern but there are no clear clues of underlying etiology. Some of these patients might have suffered cardiogenic embolization, although how large proportion of these patients is poorly known.

Left ventricular (LV) ejection fraction (EF) is considered as one of the most basic methods of measuring systolic function. However, there are also many other parameters for LV functional analysis, such as global longitudinal strain (GLS) and mitral annular plane systolic excursion (MAPSE).[3,4] Severe systolic failure is considered an established high-risk source of cardioembolism, although the thrombosis risk stratification in systolic heart failure is currently based merely on LVEF.[5,6]

We sought to explore, in a pilot case-control study, whether there are advanced echocardiography measures of systolic function signaling an increased risk for ischemic stroke among young patients with cryptogenic ischemic stroke.

2 | MATERIALS AND METHODS

2.1 | Study population

All participants in this substudy were recruited from the Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome study (SECRETO, NCT01934725). The study protocol has been published in more detail previously.[7] The inclusion criteria required an imaging-proven brain infarction. Brain magnetic resonance imaging, imaging of intracranial and extracranial arteries with either computed tomography angiography or magnetic resonance angiography was performed on all patients. No patients with causally relevant aortic or carotid pathology were included. Cardiac imaging including standardized transthoracic and transesophageal echocardiography was performed to rule out established high-risk cardiac causes of ischemic stroke.[8] Patients with prior PFO closure were excluded from this substudy. We screened for AF with ≥24-hour Holter monitoring, and none of the included patients had AF.

Patients were age- and sex-matched to stroke-free controls in a 1:1 fashion. A list of twenty potential controls per one patient were randomly identified from the Population Registry, with an invitation letter sent to controls one-by-one. If this strategy did not result in a fit willing control person, patients' nonrelated proxies or proxies of the study personnel were recruited. Detailed clinical history was recorded from all study subjects, including arterial blood pressure, height, weight, alcohol consumption, and the presence of right-to-left shunt. More detailed methods on the definitions of these have been published earlier.[9] Patients and controls were examined for the presence of right-to-left shunt (RLS) using the transcranial Doppler (TCD) bubble test with 10 mL of agitated saline-blood solution, both at rest and with the Valsalva maneuver.

All patients and controls were examined for this substudy between December 2013 and May 2017. Written informed consent was obtained from all study subjects. The study was approved by the Ethics Committee of Helsinki and Uusimaa Hospital District.

2.2 | Echocardiography methods

J.Pi examined all patients and control subjects with a General Electric Vivid E9 version 113 cardiac ultrasound device, using M5Sc and 4V probes (General Electric). The 4V probe has a possibility to electronically rotate the imaging plane. This property was utilized in apical long-axis imaging to ensure the same optimal axis in all three apical planes. J.Pi. was blinded to case-control status at the time of echocardiography and image analysis.

Basic LV measurements were obtained from the parasternal long-axis view. Other measurements were obtained from the apex. The apical 4-chamber view was defined as long-axis transsecting the LV apex and the mitral orifice, and maximizing the right ventricular area. The 2-chamber view was defined as a counter-clockwise virtual rotation of 60°, hence viewing the LV and the LA. The 3-chamber view was defined as a further counter-clockwise virtual rotation of 60°, hence viewing the LV, the ascending aorta, and the LA. LV dynamic volumetry measurements were obtained from an apical view using multi-beat 4D acquisition of six cardiac cycles, zoomed in for only the LV, obtaining approximately 50 volumes per second (vps).

Based on dynamic volumetry, we measured LV ejection fraction, calculated as (end-diastolic volume – end-systolic volume) / (end-diastolic volume). Utilizing dynamic volumetry, we also performed volume change rate analysis: volume change between all successive volume points were calculated and divided by sampling cycle length $dV_n/dt_n = (V_{n+1} - V_n)/(t_{n+1}-t_n)$. The resulted volume change rate was defined to occur at average time between the volumetric data points, from which it was calculated. Volume change rate - time and volume change rate – volume curves were generated to describe LV function. We derived the following parameters from volume change rate analysis: absolute peak emptying rate (the peak volume change rate during systole), relative peak emptying rate (absolute peak emptying rate divided by LV end-diastolic volume), time to peak emptying rate (the time from start of emptying to peak volume change), and adjusted time to peak emptying rate (time to peak emptying rate divided by length of cardiac cycle) (Figure 1).

Strain and strain rate were analyzed as a mean of all three apical planes, with a minimum requirement of twelve out of eighteen successfully measured segments, using 2D speckle tracking function. Each apical plane was analyzed as an entity, and the global values were averages of all planes (Figures 2 and 3).

Mitral annular displacement (MAD) was measured with the tissue velocity imaging-derived tissue tracking function.[10] MAD was measured from both mitral annular points in all three apical views, hence constituting six measurement points, the measurement values

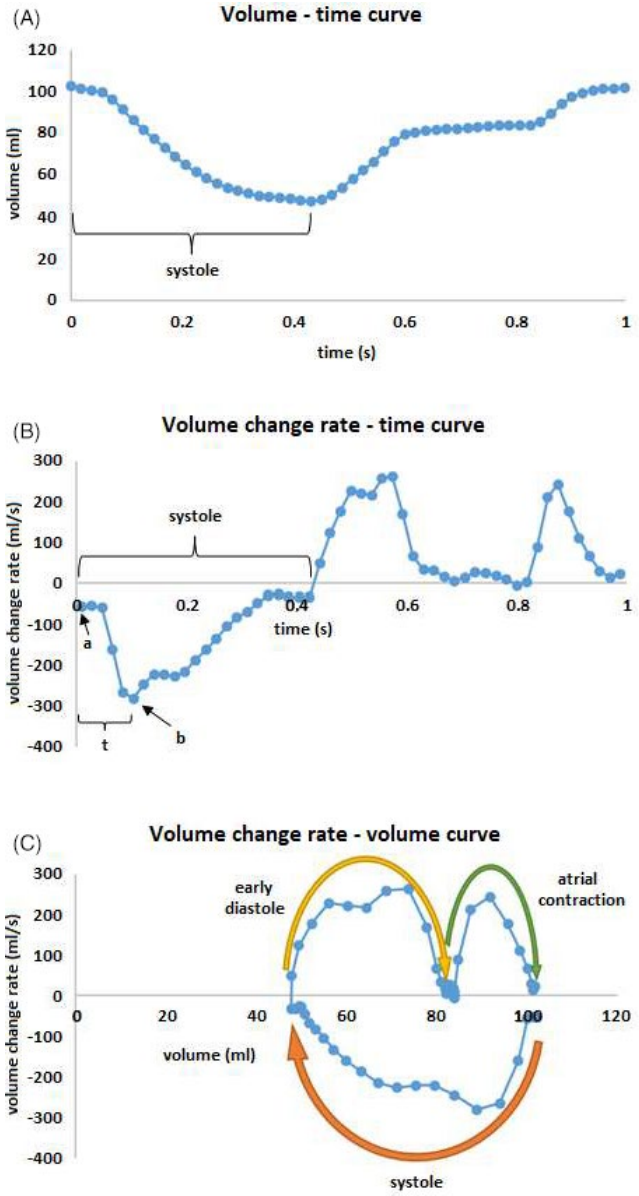

FIGURE 1 Left ventricular dynamic 3D volumetry. (A) Volume-time data exported from EchoPAC 4D LVQ software plotted as a volume-time curve. (B) Volume change rate – time curve. (C) Volume change rate - volume curve. The negative peak (b) during early systole represents absolute peak emptying rate. The time (t) from beginning of contraction (a) to peak emptying (b) represents time to peak emptying rate

of which were then averaged (Figure 4). Septal S' was measured using TDI PW from the basal ventricular septum, approximately 1 cm toward the apex from the septal mitral annulus.[11]

2.3 | Statistical methods

We used the Wilcoxon signed rank test for examining difference in continuous parameters between groups. For dichotomous parameters, we used McNemar's test. We tested the effect of RLS on systolic measurements by comparing all test subjects with RLS to all test subjects without, using the Mann-Whitney U test. We performed spearman correlation calculations with clinical parameters for the statistically significant echocardiography finding. All analyses used IBM SPSS 22 (IBM).

3 | RESULTS

3.1 | Baseline characteristics

Compared with controls, patients had a higher body weight, larger body-mass index and body surface area, and they were more frequently heavy drinkers. There were no significant differences between cases and controls in body height or blood pressure measured on the day of echocardiography (Table 1). In the stroke patients, median time from stroke onset to advanced echocardiography was 24 months (range 13-48 months). TCD bubble test was performed in 29 of 30 patients and in all controls. The patient who had not undergone TCD bubble test had RLS diagnosed by TEE. There tended to appear more RLS in the patients ($P = .065$).

3.2 | Performance of measurements

Basic LV measurements, LVEF, septal S', and triplane MAD were successful in 29 case-control pairs. Speckle tracking strain analysis was successful in 28 case-control pairs and strain rate analysis in 27 pairs. LV dynamic volumetry sufficient for volume change analysis was successful in 51 of 60 subjects, constituting 21 case-control pairs.

3.3 | Comparison of LV measures in cases and controls

There were no statistically significant differences in basic LV measures, nor in S' or LV dynamic volumetry-derived measures between cases and controls. Peak systolic longitudinal strain was significantly lower in patients than in controls ($P = .010$), and there was a trend toward lower MAD in the stroke patient group ($P = .092$). There was no statistically significant difference in peak systolic longitudinal strain rate (Table 2).

In the comparison of subjects with and without RLS, the only significantly differing systolic parameter was MAD (14.2 mm [IQR 1.8 mm] without RLS vs 13.3 mm [IQR 2.6 mm] with RLS, $P = .014$) (data not shown).

3.4 | Comparison between clinical characteristics and global longitudinal strain

Since the only echocardiographic parameter differing significantly between patients and controls was GLS, we performed Spearman correlation analyses on correlation between GLS and the clinical characteristics of patients and controls. In order to avoid confusion

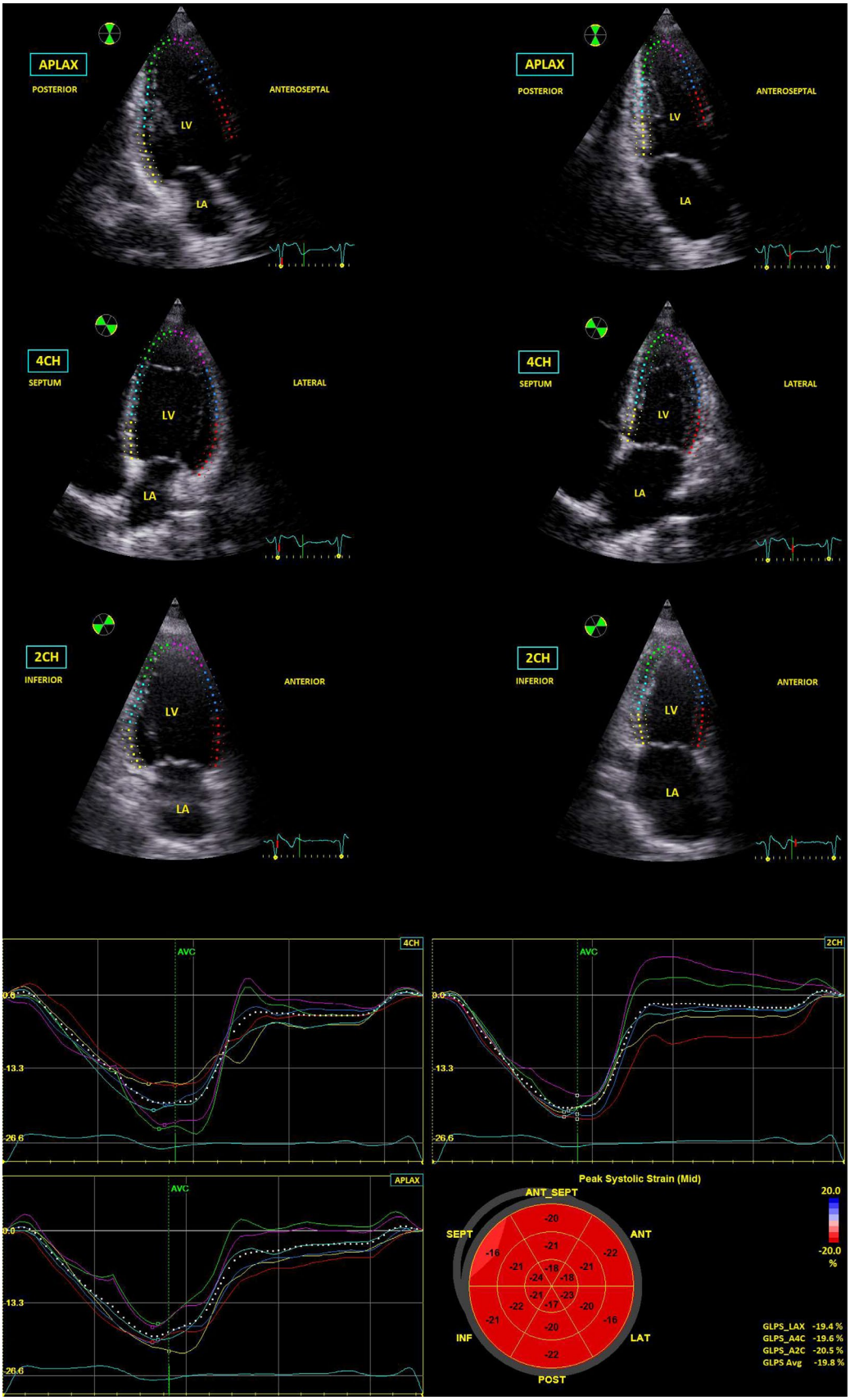

FIGURE 2 Triplane 2D speckle tracking strain analysis during diastole (left) and systole (right) in apical 3-chamber (APLAX), 4-chamber, and 2-chamber views. Peak systolic strain analysis and bullseye plot of the left ventricle (lower). The peak strain was −19.4% in the 3-chamber view, −19.6% in the 4-chamber view, and −20.5% in the 2-chamber view. Hence, global longitudinal strain was −19.8%

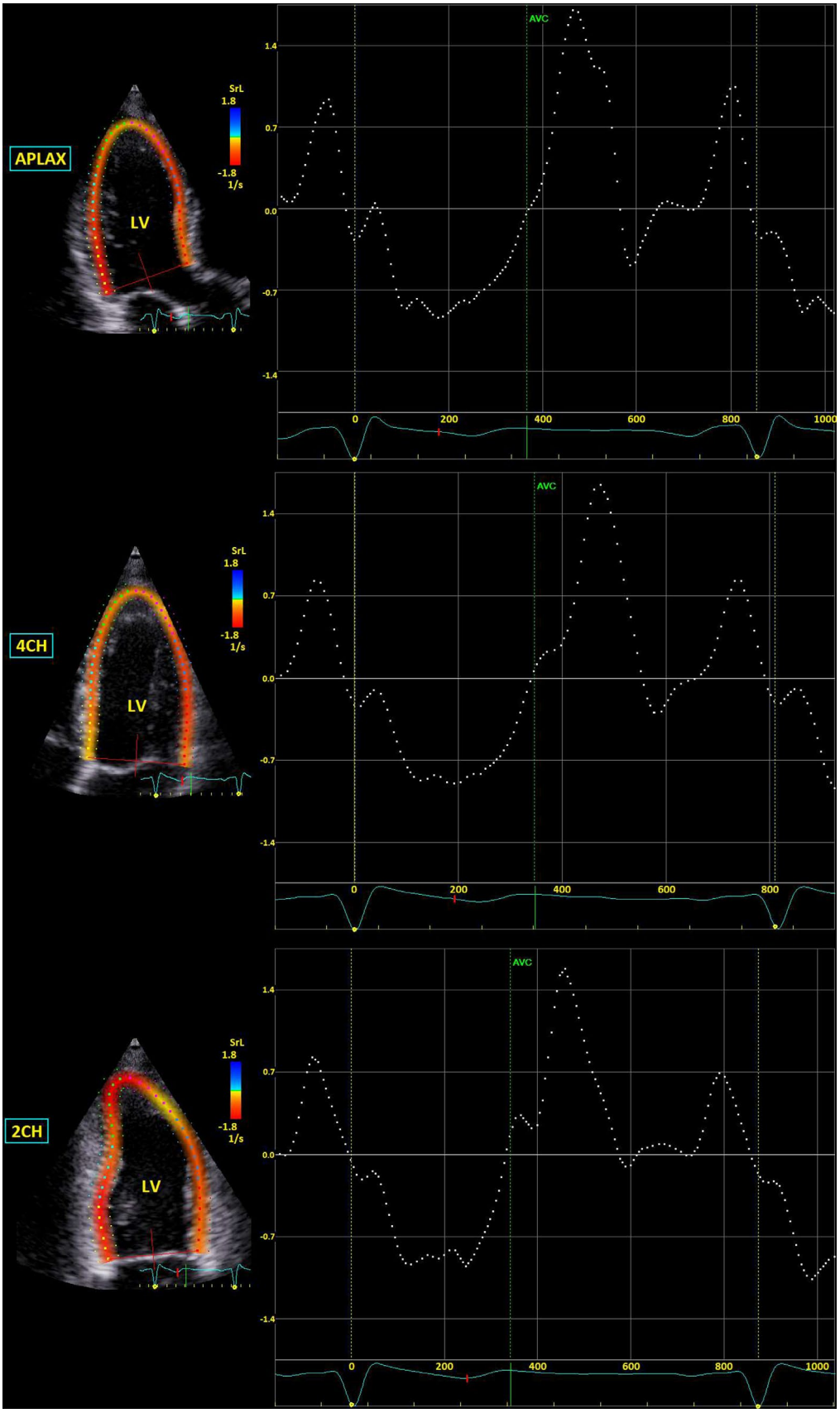

FIGURE 3 Strain rate analysis in the apical 3-chamber (APLAX), 4-chamber and 2-chamber views. The yellow line at the left QRS complex marks the beginning of systole, and the green line with the AVC (for aortic valve closure) text marks the end of systole. The peak systolic strain rate for this patient was −0.97/s in the 3-chamber view, −0.94/s in the 4-chamber view, and −0.97/s in the 2-chamber view. Hence global systolic strain rate was −0.96/s

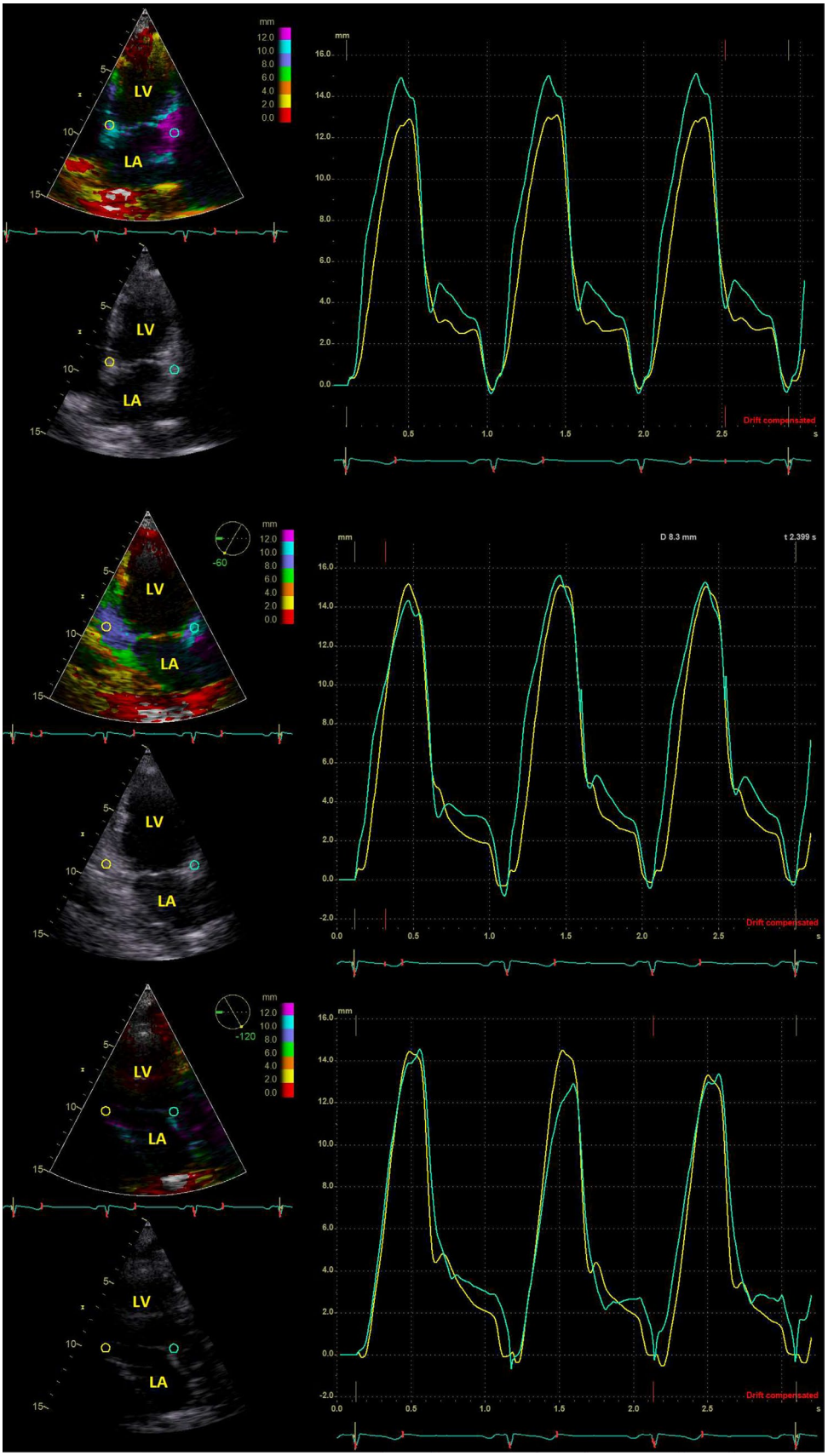

FIGURE 4 Triplane mitral annular displacement (MAD) using tissue tracking. MAD was 15.0 mm laterally and 13.0 mm septally (4-chamber view, upper row), 15.2 mm anteriorly and 15.0 mm inferiorly (2-chamber view, middle row), 13.6 mm anteroseptally and 14.1 mm posteriorly. Hence, the mean triplane MAD derived from six measurement points was 14.3 mm

with double negatives, we used the absolute amount of GLS. We found that a stronger GLS has a moderate negative correlation with height, weight, waist circumference, BMI, BSA, and male sex. The correlation was negative but weak with systolic and diastolic blood pressure measured at the day of echocardiography. No other cardiovascular risk factors than male sex had a statistically significant correlation with GLS (Table 3).

TABLE 1 Clinical characteristics of patients and controls

	Patients	Controls	*P*-value
Body measurements			
Height	172 (14)	168 (16)	.069
Weight	86.8 (30)	75.5 (27)	.012
Waist circumference	98.8 (19.8)	88.5 (19.9)	.015
Body-mass index	30.2 (7.2)	26.1 (6.7)	.026
Body surface area	2.04 (0.44)	1.88 (0.41)	.007
Systolic blood pressure	128 (21)	129 (21)	.256
Diastolic blood pressure	86 (14)	82 (15)	.303
Age at echocardiography	43 (12)	44 (13)	.098
Cardiovascular risk factors			
Male sex	15 (50)	15 (50)	1.000
Hypertension	9 (30)	4 (13)	.227
Diabetes mellitus, type 1	1 (3.3)	0	N/A
Current smoking	9 (30)	11 (37)	.774
Excessive alcohol use	9 (30)	3 (10)	.031
Physical inactivity	4 (13)	4 (13)	1.000
Right-to-left shunt	19 (63)	12 (40)	.065

Note: Body measurements: numbers are median (interquartile range). Cardiovascular risk factors: numbers are n (%).

4 | DISCUSSION

Our results suggest that a less vigorous LV longitudinal contraction is associated with increased stroke risk at younger ages. A reduced GLS has earlier been linked to an increased risk of cardiovascular events in a population of wide age range, which is well in accordance with our results.[12] However, to the best of our knowledge, our study is the first to display this association specifically for early-onset cryptogenic ischemic stroke.

Reduced systolic function has earlier been associated with hypertension in young and middle-aged (18-60 years) stroke patients, although studied in a population of mixed stroke etiology.[13] In our study population, there indeed was a positive trend towards more hypertension in the stroke patient group, although we found no actual correlation between diagnosis of hypertension and GLS in our study population. Also, the higher BMI in the stroke patient group may explain the lower GLS, since a larger mass of visceral fat is associated with lower GLS in patients with no overt heart disease.[14] Also our population showed a moderate correlation between weaker GLS and higher BMI (Table 3). Since

TABLE 2 Comparison of left ventricular systolic function parameters between patients and controls

Parameter (number of pairs)	Patients	Controls	*P*-value
Basic LV measurements			
LV maximum internal diameter (diastolic), mm (29)	49 (7)	50 (8)	.413
Interventricular septum diameter (diastolic), mm (29)	10 (2)	10 (2)	.609
LV posterior wall diameter (diastolic), mm (29)	8 (8–10)	9 (7–10)	.776
LV maximum internal diameter (systolic), mm (29)	33 (7)	31 (7)	.306
LV volumetry			
LV ejection fraction, % (29)	62 (14)	59 (15)	.462
Absolute peak emptying rate, mL/s (21)	342 (132)	309 (141)	.357
Relative peak emptying rate, EDV/s (21)	0.31 (0.07)	0.28 (0.07)	.149
Time to peak emptying rate, ms (21)	122 (42)	151 (48)	.394
Adjusted time to peak emptying rate (21)	0.12 (0.06)	0.15 (0.05)	.244
LV longitudinal contraction measurements			
Septal S' (29)	8.7 (1.5)	8.6 (1.5)	.776
Mitral annular displacement, mm (29)	13.4 (2.1)	14.3 (2.4)	.092
Peak systolic strain, % (28)	−18.9 (3.3)	−20.0 (2.8)	.010
Peak systolic strain rate, 1/s (27)	−0.91 (0.23)	−0.96 (0.12)	.416

Note: Numbers are median (interquartile range).
P-values by Wilcoxon signed rank test.
Abbreviations: EDV = end-diastolic volume; LV = left ventricular

TABLE 3 Correlation between absolute amount of GLS and clinical characteristics

	Correlation	*P*-value
Body measurements		
Height	−0.477	<.001
Weight	−0.658	<.001
Waist circumference	−0.584	<.001
Body-mass index	−0.551	<.001
Body surface area	−0.667	<.001
Systolic blood pressure	−0.379	.003
Diastolic blood pressure	−0.355	.006
Age at echocardiography	−0.301	.022
Cardiovascular risk factors		
Male sex	−0.427	<.001
Hypertension	−0.139	.297
Diabetes mellitus, type 1	−0.075	.575
Current smoking	−0.081	.545
Excessive alcohol use	−0.248	.060
Physical inactivity	0.104	.439
Right-to-left shunt	−0.153	.252

Note: Numbers are spearman coefficients.

GLS did not differ between subjects with and without RLS, nor did RLS significantly correlate with GLS, the difference is probably not explained by patients having higher prevalence of RLS. Whether a lower GLS actually contributes to clot formation, or is merely a substitute marker for stroke risk factors such as obesity, is unclear. One possible way of weak GLS contributing to increased clot formation is slight stagnation of blood flow in the LV. However, our finding is merely a perspective on disease mechanism, and the level of GLS should not cause any modification in stroke treatment.

Global longitudinal strain is known to be diminished in the acute phase of ischemic stroke, although recovering markedly within 10 days, a time much shorter than the delay from stroke onset to investigational echocardiography in our study.[15] Furthermore, the same study found diminished GLSR in the acute phase, which is not the case for our patients compared with controls. Hence, the effect of suffered stroke is not per se a probable explanation for our finding.

Volumetry-derived parameters, such as EF, absolute peak emptying rate and time to peak emptying rate, did not differ between our patients and controls. The lack of differences in these measures suggests a merely subclinical myocardial dysfunction in our patients, a condition similar to early stages of cardiotoxic reactions, seen in both cardiotoxic drugs and the early stages of alcoholic cardiomyopathy. The pattern of less vigorous but still normal GLS is in line with mild cardiotoxicity underlying subclinical myocardial dysfunction.[16,17] However, although the patients in our population were more frequently heavy drinkers than the controls, the causality is very unclear, since the correlation between heavy drinking and weaker GLS was weak and of uncertain statistical significance (Table 3).

We have introduced several novel methods of measuring LV systolic function, although none of these seem to be as sensitive to detect minor cardiac abnormalities as GLS in our study population. Absolute peak emptying rate and time to peak emptying rate are modifications of peak filling rate and time to peak filling rate, parameters formerly introduced to measure diastolic function.[18,19] Also, the measurement of MAD around the entire mitral annulus from 6 points, is to our knowledge a novel method, and it also found a positive trend in our study, signaling it mimicks GLS. This novel method could be of use in examining LV longitudinal contraction of patients with visibility too limited for triplane GLS. MAD showed a trend of weaker contraction in stroke patients, although both are patients and controls had mostly normal MAD (medians 13.4 mm vs 14.3 mm), compared with the normal limit of >12 mm in the MYDISE study.[20] S' did not differ between our patients and controls, and was clearly normal in both groups compared with normal limits in the MYDISE study: our patients and controls had medians over 8 cm/s peak basal septal velocity, whereas the normal limit is 6.4 cm/s.[21]

Strengths of the study include a well-defined and widely clinically investigated patient population, a thorough echocardiography protocol with advanced methods, and all echocardiography performed by the same echocardiographist blinded to clinical data. Limitations include a small sample size, and hence also the inability to perform multivariate analysis. Therefore, the findings of our pilot study should be further explored in a larger sample.

5 | CONCLUSIONS

There are subtle differences in longitudinal systolic function between young cryptogenic stroke patients and healthy controls. The difference might partially be mediated by hypertension, obesity, or heavy drinking among young cryptogenic stroke patients. Volumetry-derived measures do not seem to differ in these groups.

CONFLICT OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Pirinen J, Sinisalo J, Putaala J, and Järvinen V conceived and designed the study. Pirinen J and Kuusisto J analyzed and interpreted the data. Pirinen J drafted the article. Kuusisto J, Martinez-Majander N, Sinisalo J, Pöyhönen P, Putaala J, and Järvinen V crtically revised the article. All authors gave approval for the submission of article. Pirinen J and Pöyhönen P involved in statistical analysis. Pirinen J and Putaala J obtained and secured funding. Pirinen J and Martinez-Majander N collected the data. We also wish to thank Laura-Leena Kupari, RN, for all her efforts in assisting this study.

DATA AVAILABILITY STATEMENT

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

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