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# Diastolic function in young patients with cryptogenic stroke: A case–control pilot study

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## Abstract

**Background:** Ischaemic stroke in young individuals often remains cryptogenic. In this pilot study, we investigated, whether advanced echocardiography methods could find differences in the diastolic function between young cryptogenic stroke patients and stroke-free controls.

**Methods:** We recruited 30 cryptogenic ischaemic stroke patients aged 18–49 and 30 age- and sex-matched stroke-free controls among participants of the Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome (SECRETO) study (NCT01934725). We measured diastolic function parameters derived from speckle tracking strain rate, Doppler techniques and 4D volumetry. We also performed statistical analyses comparing only the highest and lowest tertile of cases and controls for each parameter.

**Results:** None of our patients or controls had diastolic dysfunction according to ASE/EACVI criteria. However, compared to stroke-free controls, the stroke patient group had lower E/A ratio of mitral inflow, lower lateral and mean e', lower A/a' ratio, lower strain rate in early diastole and lower speckle tracking-derived e/a ratio. When comparing the lowest tertiles, patients also had a lower peak filling rate by 4D volumetry, a lower peak early filling fraction (fraction of left ventricular filling during early diastole), and lower velocities in a series of the tissue Doppler-derived diastolic parameters and blood flow/tissue velocity ratios.

**Conclusion:** Our study displayed subtle differences in diastolic function between patients and stroke-free controls, which may play a role in early-onset cryptogenic stroke. The differences were clearer when the lowest tertiles were compared, suggesting that there is a subgroup of young cryptogenic stroke patients with subclinical heart disease.

KEYWORDS

4D volumetry, brain infarction, echocardiography, strain imaging, strain rate imaging

## 1 | INTRODUCTION

Ischaemic stroke can occur due to cardioembolism. Some cardiac diseases are categorized as high-risk sources of cardioembolism, due to an over 2% annual ischaemic stroke risk (Ay et al., 2005). Part of ischaemic strokes remains cryptogenic, that is with undetermined aetiology despite intensive diagnostic investigations. Stroke at younger ages particularly often remains cryptogenic (Putaala et al., 2012). A portion of these strokes are probably of cardiac origin, although how large this portion is, is unknown.

Cardiac findings in particularly young (below 50 years) cryptogenic stroke patients have been described very scarcely in the literature. In older patients, altered diastolic function is associated with a higher risk of left atrial appendix thrombosis in patients with atrial fibrillation (AF), and diastolic dysfunction is associated with worse outcome after ischaemic stroke (Doukky et al., 2016; Garshick et al., 2018; Park et al., 2016).

We sought to evaluate, whether advanced echocardiography methods can detect differences in left ventricular diastolic function between young cryptogenic stroke patients and stroke-free controls, and hence detect whether diastolic function could play a role in cryptogenic stroke in the young.

## 2 | MATERIALS AND METHODS

### 2.1 | Study population

Participants in this study were recruited among those enrolled into the Searching for Explanations for Cryptogenic Stroke in the Young: Revealing the Etiology, Triggers, and Outcome study (SECRETO, NCT01934725), which is an international prospective multicentre case–control study of young adults (age 18–49) with a first-ever ischaemic stroke of undetermined aetiology. The study protocol has earlier been published in more detail (Putaala et al., 2017). Written informed consent was obtained from all study participants. SECRETO has been approved by the Ethics Committee of Helsinki and Uusimaa Hospital District.

Patients were included after standardized diagnostic procedures, including brain magnetic resonance imaging, imaging of intracranial and extracranial arteries with either computed tomography angiography or magnetic resonance angiography, and cardiac imaging to rule out established causes of ischaemic stroke. Cardiac imaging included standardized transthoracic and transesophageal echocardiography (Saeed, Gerdts, Waje-Andreassen, Sinisalo, & Putaala, 2019). We ruled out AF with a ≥ 24-hr Holter monitoring. Patients were classified according to embolic stroke of undetermined source (ESUS) criteria as ESUS (+) and ESUS (–) (Hart et al., 2014). Body surface area (BSA) was calculated using the Mosteller formula (Mosteller, 1987). Patients included in the present study suffered their stroke between December 2013 and May 2017.

Patients were age- and sex-matched to stroke-free controls in a 1:1 fashion. Controls were searched randomly through population registers, and in some cases patients' nonrelated proxies. 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. The definition of right-to-left shunt was a positive finding (any degree of shunt) on either transesophageal echocardiography or transcranial Doppler bubble test; each patient and control underwent at least one of these tests. Participants were dichotomized according to their right-to-left shunt status. Patients with prior PFO closure were excluded from the study.

Detailed baseline data and clinical data and basic left ventricular (LV) measurements have been published earlier (Pirinen et al. 2020). Compared with controls, patients were heavier, had a larger waist circumference, higher body-mass index (BMI) and a larger BSA. Patients also had a higher prevalence of right-to-left shunt. We found no significant differences between patients and controls regarding established cardiovascular risk factors. There were no differences between the two groups in basic LV diameter, LV wall thickness or LV ejection fraction.

### 2.2 | Echocardiography methods

We performed advanced echocardiography on our study subjects between November 2017 and October 2018. The same echocardiographist (J.Pi) examined all patients and control subjects blinded to the case–control status and clinical data, with a General Electric Vivid E9 version 113 cardiac ultrasound device, using M5Sc and 4V probes (General Electric).

Measurements of mitral inflow E wave and A wave were obtained from the apical 4-chamber view, as were e' and a' according to international standards (Nagueh et al., 2016). We calculated E/e', A/a' and E'/a' for all combinations of septal, lateral and mean measurements. The diastolic function was evaluated according to ASE/EACVI criteria (Nagueh et al., 2016).

Left ventricular strain rate analysis was derived from the apical 4-chamber, 2-chamber and 3-chamber views, using speckle tracking imaging. Only the longitudinal component of strain rate was analysed. A true apical angle was verified using the triplane mode, with which the echocardiographist can confirm that both the apex and the mitral valve orifice are in the midline of the ultrasound beam in all three planes simultaneously. The apical 4-chamber view was defined as a view with centre in LV apex and the mitral orifice, viewing both ventricles and both atria, with a rotation angle maximizing the area of the right ventricle (RV). The 2-chamber view was defined as a counter-clockwise virtual rotation of 60° from the 4-chamber view, hence viewing the LV and the left atrium (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. The typical frame rate used for this imaging was 60–80 fps. Strain rate was measured using speckle tracking from 2D images. Global strain rate was defined as a mean of the entire LV strain rate in the three apical views. Strain rate

was measured in two different time points: in early diastole and in late diastole (during atrial contraction), using EchoPAC version 113 (General Electric) (Figure 1).

Left ventricular volume data points with respective time stamps over whole cardiac cycle were exported from Echopac software to sheet data. From these data, volume change rate was calculated: volume change between all successive volume points was calculated and divided by sampling cycle length $dV_n/dt_n = (V_n + 1 - V_n)/(t_n + 1 - t_n)$. For this average, time between these two data points was used ($t_m$). Volume change rate curves were then generated (Figure 2). Early positive peak represented peak early filling rate, as earlier described by Hieda, and latter positive peak late peak filling rate (Hieda et al., 2018). Time to peak early filling rate was determined both in milliseconds and relative time

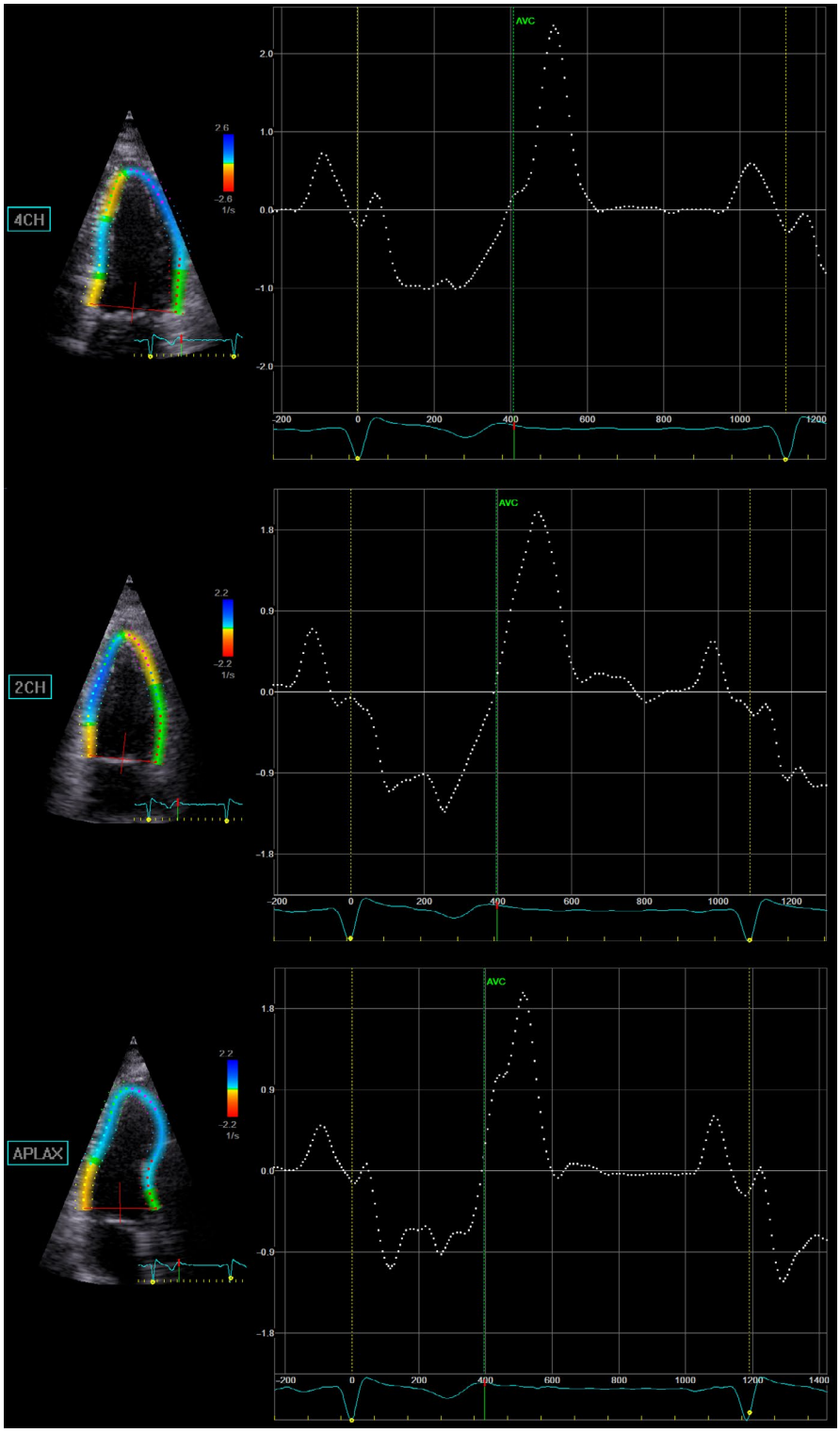


**FIGURE 1** Left ventricular strain rate analysis in 4-chamber view (upper), 2-chamber view (middle) and 3-chamber view (lower). The early diastolic maximum strain rates of this control person in the three views were 2.36/s, 1.94/s and 1.93/s. The late diastolic peak strain rates were 0.59/s, 0.55/s and 0.58/s, respectively. Hence, the global early diastolic strain rate was 2.08/s, global late diastolic strain rate was 0.57/s, and the speckle tracking e/a ratio 3.65. The yellow lines mark the end of diastole, and the green line marks aortic valve closure, and hence the end of systole

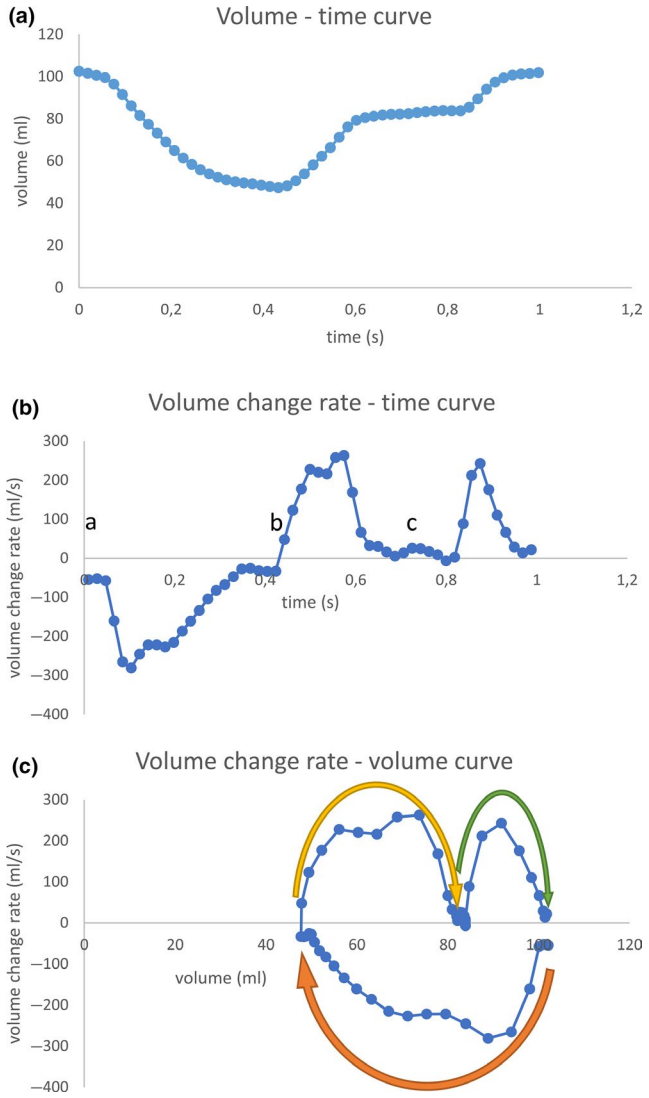


**FIGURE 2** Analysis of left ventricular volume dynamics. (A) Volume and time data exported from EchoPac 4D LVQ software and plotted as volume–time curve. From these data, volume change rate is calculated and displayed as (B) volume change rate–time, and (C) volume change rate –volume curves. In figure B, early positive peak represents early peak filling rate. In figure C, the red arrow depicts ventricular systole (from a to b), the yellow arrow early systole (b to c) and the green arrow late diastole during atrial contraction (c to a). Point a represents end-diastolic volume, b end-systolic volume, and c mid-diastolic volume after early filling

of the whole cardiac cycle. Volume change rate–volume curves were also generated. These curves were used to detect LV volumes after early filling to calculate early filling fraction.

### 2.3 | Statistical methods

We used the Wilcoxon signed rank test for all continuous parameters. For dichotomous clinical parameters, we used the McNemar test. Tertile analyses were performed using Wilcoxon signed rank test, selecting only the minimum or maximum tertile of case and control measurements of each parameter, and comparing these. All analyses used IBM SPSS 22 (IBM), or RStudio 1.2.1335 (RStudio).

## 3 | RESULTS

### 3.1 | Performance of measurements

Heart rate during echocardiography varied between 39/min and 87/min in our subjects. LV 4D volumetry, to a degree acceptable for flow analysis, was successful in 51 of 60 subjects, constituting 21 case–control pairs. Mitral inflow E and A, and the measurement of septal and lateral e' and a', could be obtained in all subjects. Speckle tracking strain rate analysis was successful in 27 case–control pairs.

### 3.2 | Analysis of LV diastolic function

None of the patients or controls had evident diastolic dysfunction according to American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACVI) criteria. Controls had higher mitral inflow E/A ratio than patients, and larger mean e'. In strain rate analysis, both early diastolic strain rate (e), and the ratio between early diastolic and late diastolic strain rate (e/a), were higher in controls than in patients (Table 1).

### 3.3 | Minimum and maximum tertile analysis of diastolic parameters

In minimum tertile analysis, stroke patients had a lower E/A ratio, lower E wave velocity, lower septal e' velocity, lower mean e', lower e'/a' ratio regardless of measurement point, lower septal A/a' ratio, and also lower peak early filling rate, time to peak filling rate and early filling fraction (Table 2). In maximum tertile analysis, controls had a higher E/A ratio, higher septal e', whereas stroke patients had a higher lateral a', and a higher peak filling rate in atrial systole (Table 3).

## 4 | DISCUSSION

To the best of our knowledge, this is the first study to investigate LV diastolic function in young cryptogenic stroke patients. Our observations support the hypothesis that diastolic function has a role in the pathogenesis of ischaemic stroke. However, the relationship between diastolic parameters and stroke has been only scarcely studied to date, with only a few reports showing positive associations, mostly in the presence of AF (Doukky et al., 2016; Garshick et al., 2018; Park et al., 2016).

Our main result is that even without actual diastolic dysfunction, there seems to be an association between poorer values of diastolic function parameters and ischaemic stroke, since the stroke patient group had a lower E/A ratio, lower mean e' velocity, and lower peak

**TABLE 1** Comparison of echocardiographic findings between stroke patients and controls

| Mitral inflow measurements | Patients | Controls | *p*-value |
|---|---|---|---|
| E wave maximum velocity, m/s | 0.8 (0.3) | 0.7 (0.2) | .424 |
| E wave deceleration time, ms | 160 (40) | 160 (40) | .896 |
| A wave maximum velocity, m/s | 0.6 (0.2) | 0.5 (0.2) | .081 |
| E/A ratio | 1.4 (0.8) | 1.5 (1.1) | .039 |
| Mitral annulus tissue Doppler imaging | | | |
| Septal e', cm/s | 11.0 (3.0) | 11.5 (4.0) | .074 |
| Lateral e', cm/s | 13.0 (5.0) | 14.0 (5.0) | .039 |
| Mean e', cm/s | 12.0 (2.7) | 13.3 (4.3) | .016 |
| Septal a', cm/s | 8.0 (3.0) | 8.0 (2.0) | .680 |
| Lateral a', cm/s | 7.0 (4.0) | 8.0 (2.0) | .830 |
| Mean a', cm/s | 9.5 (3.4) | 9.8 (2.0) | .206 |
| Septal e'/a' | 1.3 (0.8) | 1.4 (0.7) | .247 |
| Lateral e'/a' | 1.9 (1.1) | 1.9 (1.0) | .136 |
| Mean e'/a' | 1.6 (1.0) | 1.7 (0.8) | .102 |
| Mitral inflow/ annulus tissue Doppler ratios | | | |
| Septal E/e' | 6.9 (2.1) | 6.3 (2.3) | .737 |
| Lateral E/e' | 5.8 (2.0) | 5.4 (2.0) | .399 |
| Mean E/e' | 6.2 (2.0) | 5.8 (2.2) | .341 |
| Septal A/a' | 7.0 (3.8) | 6.0 (3.3) | .073 |
| Lateral A/a' | 7.4 (2.8) | 6.3 (2.6) | .094 |
| Mean A/a' | 6.8 (2.7) | 6.2 (2.9) | .047 |
| Left ventricular strain rate analysis | | | |
| Peak e strain rate, $1/s^2$ | 1.4 (0.4) | 1.5 (0.5) | .005 |
| Peak a strain rate, $1/s^2$ | 0.7 (0.3) | 0.7 (0.2) | .755 |
| Peak strain rate e/a | 2.1 (1.4) | 2.2 (1.0) | .013 |
| Left ventricular 4D volumetry | | | |
| Peak early filling rate, ml/s | 277 (148) | 303 (108) | .289 |
| Time to peak early filling rate, ms | 79 (50) | 88 (39) | .322 |
| % time to peak early filling rate | 89 (70) | 95 (63) | .339 |
| Peak filling rate in atrial systole, ml/s | 225 (128) | 207 (66) | .076 |
| Early filling fraction, % | 71 (16) | 70 (8) | .658 |

*Note:* Numbers are median (interquartile range).

**TABLE 2** Lowest tertile analysis of echocardiographic parameters between stroke patients and controls

| Mitral inflow measurements | Patients | Controls | *p* |
|---|---|---|---|
| E wave maximum velocity, m/s | 0.5 (0.2) | 0.6 (0.1) | .005 |
| E wave deceleration time, ms | 130 (20) | 130 (20) | .907 |
| A wave maximum velocity, m/s | 0.4 (0.1) | 0.3 (0.11) | .040 |
| E/A ratio | 0.9 (0.1) | 1.1 (0.1) | .006 |
| Mitral annulus tissue Doppler imaging | | | |
| Septal e', cm/s | 8 (1) | 9.5 (1) | .015 |
| Lateral e', cm/s | 10.5 (1.8) | 11.5 (2.5) | .097 |
| Mean e', cm/s | 9.5 (1.5) | 10 (0.9) | .031 |
| Septal a', cm/s | 6.5 (1.8) | 7 (1) | .587 |
| Lateral a', cm/s | 6 (0.8) | 6 (2.5) | .968 |
| Mean a', cm/s | 8 (0.8) | 8.8 (0.5) | .039 |
| Septal e'/a' | 0.8 (0.14) | 1.0 (0.1) | .005 |
| Lateral e'/a' | 1.0 (0.2) | 1.3 (0.4) | .015 |
| Mean e'/a' | 1.0 (0.1) | 1.3 (0.2) | <.001 |
| Mitral inflow/ annulus tissue Doppler ratios | | | |
| Septal E/e' | 5.4 (1.2) | 5.4 (0.5) | .791 |
| Lateral E/e' | 4.4 (0.6) | 4.3 (0.6) | .271 |
| Mean E/e' | 4.9 (0.7) | 4.6 (0.5) | .272 |
| Septal A/a' | 4.8 (0.5) | 4.3 (0.5) | .009 |
| Lateral A/a' | 5.3 (0.9) | 4.5 (1.2) | .130 |
| Mean A/a' | 5.2 (0.8) | 4.5 (0.9) | .028 |
| Left ventricular strain rate analysis | | | |
| Peak e strain rate, $1/s^2$ | 0.8 (0.3) | 1.1 (0.3) | .028 |
| Peak a strain rate, $1/s^2$ | 0.5 (0.2) | 0.5 (0.2) | .448 |
| Peak strain rate e/a | 1.1 (0.3) | 1.5 (0.7) | .043 |
| Left ventricular 4D volumetry | | | |
| Peak early filling rate, ml/s | 223.5 (63.3) | 273.2 (51.8) | .029 |
| Time to peak early filling rate, ms | 56 (8) | 73 (22) | .014 |
| % time to peak early filling rate | 53 (19) | 65 (19) | .058 |
| Peak filling rate in atrial systole, ml/s | 179.4 (56.6) | 143.6 (37.0) | .105 |
| Early filling fraction, % | 59.9 (14.8) | 66.7 (3.1) | .004 |

*Note:* Numbers are median (interquartile range)

early diastolic strain rate and strain rate e/a ratio. The minimum tertile analysis findings of patients with lower maximum E wave velocity, higher A wave velocity, lower septal e', lower a'/e', higher A/a', lower peak early filling rate and lower early filling fraction are also suggestive that there is a subgroup of young stroke patients with poorer diastolic function than in their stroke-free counterparts. Also, the maximum tertile analysis, demonstrating higher lateral a' and peak filling rate in atrial systole in this subgroup of patients, suggests pronounced atrial contraction, possibly to compensate weakness in early filling.

Earlier, diastolic dysfunction measured by E/e' ratio has been linked to higher risk of thrombosis in patients with AF (Doukky et al., 2016; Garshick et al., 2018). Also, poorer diastolic function assessed by higher E/e' is associated with higher risk of stroke recurrence, suggesting that diastolic function is associated with the mechanisms of intracardiac thrombosis (Park et al., 2016). However, we did not find significant differences in the E/e' ratio between patients and controls, although we found differences in several other diastolic parameters. One reason for that may be that E/e' is a quite specific marker for diastolic dysfunction and elevated LV filling pressure, but lacks sensitivity (Sharifov et al., 2016). Furthermore, since all patients and controls had normal diastolic function according to ASE/EACVI criteria and normal E/e' values, the association between E/e' and LV filling pressure may not be accurate.

**TABLE 3** Highest tertile analysis of echocardiographic parameters between stroke patients and controls

| Mitral inflow measurements | Patients | Controls | *p* |
|---|---|---|---|
| E wave maximum velocity, m/s | 1.0 (0.1) | 0.9 (0.2) | .427 |
| E wave deceleration time, ms | 190 (15) | 185 (28) | 1.000 |
| A wave maximum velocity, m/s | 0.7 (0.1) | 0.6 (0.2) | .139 |
| E/A ratio | 1.8 (0.3) | 2.3 (0.4) | .003 |
| Mitral annulus tissue Doppler imaging | | | |
| Septal e', cm/s | 13.0 (12) | 14.5 (1.0) | .040 |
| Lateral e', cm/s | 16.0 (2.8) | 18.0 (1.8) | .079 |
| Mean e', cm/s | 14.5 (2.5) | 15.8 (1.6) | .087 |
| Septal a', cm/s | 10.5 (1.8) | 10.0 (0.8) | .163 |
| Lateral a', cm/s | 11.0 (3.0) | 9.0 (2.0) | .046 |
| Mean a', cm/s | 11.0 (0.5) | 11.3 (0.9) | .086 |
| Septal e'/a' | 2.0 (0.7) | 2.1 (0.7) | .520 |
| Lateral e'/a' | 2.5 (0.8) | 2.7 (0.3) | .343 |
| Mean e'/a' | 2.1 (0.6) | 2.4 (0.7) | .496 |
| Mitral inflow/annulus tissue Doppler ratios | | | |
| Septal E/e' | 8.9 (1.6) | 8.6 (1.2) | .423 |
| Lateral E/e' | 6.8 (1.4) | 6.7 (1.1) | .239 |
| Mean E/e' | 7.8 (0.9) | 7.3 (1.0) | .384 |
| Septal A/a' | 9.3 (1.2) | 8.0 (1.9) | .064 |
| Lateral A/a' | 9.5 (1.5) | 8.5 (1.5) | .058 |
| Mean A/a' | 9.5 (1.4) | 8.3 (0.8) | .121 |
| Left ventricular strain rate analysis | | | |
| Peak e strain rate, $1/s^2$ | 1.6 (0.3) | 1.8 (0.2) | .075 |
| Peak a strain rate, $1/s^2$ | 0.9 (0.2) | 0.8 (0.1) | .069 |
| Peak strain rate e/a | 2.8 (0.7) | 3.3 (1.9) | .272 |
| Left ventricular 4D volumetry | | | |
| Peak filling rate, ml/s | 405.1 (81.7) | 441.4 (79.7) | .529 |
| Time to peak early filling rate, ms | 110 (57) | 132 (36) | .623 |
| % time to peak early filling rate | 136 (45) | 141 (73) | .597 |
| Peak filling rate in atrial systole, ml/s | 317.1 (46.6) | 227.2 (29.7) | .002 |
| Early filling fraction, % | 75.9 (5.0) | 76.9 (6.2) | .529 |

*Note:* Numbers are median (interquartile range).

In our study, the diastolic strain rate e and strain rate e/a ratio were significantly higher in controls than patients, which suggests that the patients have stiffer LV than the controls. Our method of examining LV diastolic function with speckle tracking SR was earlier used to identify increased risk of AF among general ischaemic stroke patients (Skaarup et al., 2017). In that study, early diastolic SR was the only LV speckle tracking parameter associated with AF in ischaemic stroke patients, although they did not use our method of calculating the SR-derived e/a ratio, which was also lower in our patients than in controls.

Our patients had a higher prevalence of right-to-left shunts than the controls, which might be a confounding factor regarding stroke aetiology. However, the effect of a right-to-left shunt on diastolic function has been studied very scarcely, although one small study suggests that PFO closure, and hence the elimination of right-to-left shunt, has no effect on the diastolic E/A ratio or e' (Yalonetsky, Schwartz, & Lorber, 2007). This finding supports the theory of diastolic function being an entity independent of right-to-left shunt, and thus might play an independent role in thrombogenesis in our patients.

Based on our data, we can only hypothesize the possible underlying pathways explaining the link between diastolic dysfunction and ischaemic stroke. As our patients were more obese compared with controls, one possible explanation includes the contribution of obesity with diastolic dysfunction, hypercoagulation and occult AF.

Strengths of our study include a systematic and well-matched case–control population, a prospective design, a precise protocol with very few missing data, blinding of the echocardiographist, and the use of modern echocardiography methods such as 4D volumetry and strain rate analysis. Limitations include a relatively small sample size, which was justified with the imaging protocol being very demanding, and the purpose of the study to create new hypotheses to be tested more widely in the future. Other limitations were shortcomings inherent to case–control studies, such as selection bias.

## 5 | CONCLUSIONS

Young cryptogenic ischaemic stroke patients tend to have normal LV diastolic function. Aside from actual diastolic dysfunction, our pilot study found subtle differences in the apparently normal diastolic function between young cryptogenic stroke patients and stroke-free controls. Diastolic function may thus be one of the players in cryptogenic ischaemic stroke at young age by increasing susceptibility for intracardiac thrombosis through slower blood flow. Future studies should enrol larger patient populations to verify our inaugural observations.

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### CONFLICTS OF INTEREST

None.

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