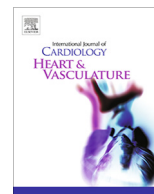




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Impairment of left atrial function and cryptogenic stroke: Potential insights in the pathophysiology of stroke in the young



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ABSTRACT

Background: Stroke is one of the leading causes of morbidity and mortality with a significant percentage classified as cryptogenic. Left atrial (LA) remodelling, a substrate for atrial fibrillation (AF) and stroke development, may play a role in identification of the aetiology of cryptogenic stroke. We aimed to examine LA function to gain mechanistic insights into the pathophysiology of cryptogenic stroke in young patients otherwise at low risk for cardiovascular disease.

Methods: Patients aged <60 years without traditional cardiovascular risk factors and who were diagnosed with ischaemic cryptogenic stroke or TIA were evaluated and compared to healthy controls and patients with paroxysmal AF with a CHA₂DS₂-VA score of 0. Conventional and novel left ventricular (LV) and LA echocardiographic parameters between the three groups were assessed.

Results: Each group consisted of thirty patients. There were no significant differences in LV parameters (LVEF, LV endoGLS) between groups. LA strain in stroke patients was significantly lower compared to the controls (median 33%; interquartile range (IQ) [32/39] vs 31 [27/34]; $p = 0.008$). LA strain was significantly lower in AF patients compared to stroke patients (median 21% [19/22] vs 31% [27/34]; $p < 0.0001$).

Conclusion: A stepwise reduction in measures of LA function was appreciated between controls, young stroke and paroxysmal AF groups. This may indicate dynamic LA remodelling occurring in the young stroke population and suggest a shared causal mechanism for stroke development in this group. LA strain may further refine the risk for cardioembolic stroke.

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1. Introduction

Although the majority of strokes affect the elderly, there has been a rise in incidence of stroke in young adults over the past decade [1,2]. This presents unique diagnostic challenges as up to 20% of this group lack classical modifiable cardiovascular risk factors

which are traditionally associated with stroke development [3]. Many of these strokes are classified as cryptogenic, whereby the exact aetiology and pathophysiology of the stroke remains elusive.

Occult paroxysmal atrial fibrillation (AF) has been proposed to be the cause of a significant proportion of cryptogenic ischaemic strokes [4]. The ASSERT study, which evaluated the incidence of subclinical atrial arrhythmias in stroke in an elder population, demonstrated a relationship between subclinical AF and an increased risk of stroke and embolism. However, interestingly there was a lack of a clear temporal relationship between arrhythmia and stroke development [5]. This suggests that there may be other causative factors which may play a role in the pathogenesis of AF and cryptogenic ischaemic stroke. While shared risk factors such as atherosclerosis and hypertension may be contributive, emerging evidence suggests that left atrial (LA) dysfunction in

Abbreviations: LVEDD, Left ventricular end diastolic diameter; LVESD, Left ventricular end systolic diameter; LVEF, Left ventricular ejection fraction; LV GLS, Left ventricular global longitudinal strain; RV, Right ventricle; TAPSE, Tricuspid annular plane systolic excursion; RVSP, Right ventricular systolic pressure; RA, Right atrial; LA, Left atrial; LAEF, Left atrial ejection fraction; LA GLS, Left atrial global longitudinal strain.

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the absence of captured AF may be associated with thromboembolism and stroke development [6–8].

Structural and functional changes in the left atrium have been linked to the pathophysiology of incident AF, ischaemic stroke and adverse cardiovascular outcomes [9,10]. Additionally, there is evidence supporting LA strain as a measure of subclinical LA dysfunction with incremental value in prediction of AF in a cryptogenic stroke cohort over traditional clinical and echocardiographic parameters [11].

Given this intricate and dynamic relationship between LA remodelling, AF and ischaemic stroke development, we propose that measures of LA function such as LA strain may serve as a biomarker for stratification of young patients with cryptogenic stroke with regards to cardioembolic stroke risk. Hence the aim of our study was to evaluate differences in cardiac chamber size and function between a cohort of young cryptogenic stroke patients, young healthy adults and those with paroxysmal AF in a young cohort without cardiovascular risk factors.

2. Methods

2.1. Study population

This a retrospective analysis of a prospectively collected study population. Young patients aged <60 years who were admitted to our institution with diagnosis of cryptogenic ischaemic stroke or transient ischaemic attack (TIA) were evaluated. Only those without traditional cardiovascular risk factors (any history of ischaemic heart disease, heart failure, hypertension, diabetes mellitus, stroke, hypercholesterolaemia, valvular or congenital) and who received transthoracic echocardiography (TTE) during their admission were included. These patients were compared to young (<60 years) healthy controls identified from referrals to our echocardiography laboratory and young (<60 years) patients with paroxysmal AF with a CHA₂DS₂-VA score of 0 identified from admissions to our service.

All patients in the stroke group received at least 24 hours of cardiac monitoring. As part of their stroke workup, these patients also underwent computed tomography and magnetic resonance imaging of the brain as well as comprehensive vascular imaging of the aortic arch, neck and cerebral vessels. The diagnosis of stroke or TIA was adjudicated by the patient's treating stroke specialist based on the Causative Classification of Ischaemic Stroke (CCS) system.

Our study was approved by the New South Wales Human Research and Ethics Committee.

2.2. Echocardiography

TTE was performed using commercially available equipment according to recommendations of the American Society of Echocardiography [12]. All echocardiographic images were saved in digital format and analysis was performed offline by two investigators blinded to the clinical history of the patients. All subjects were in sinus rhythm at the time the measurements were obtained with analysis performed using a mean of three cardiac cycles.

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 apical 4-, 3- and 2-chamber views and LV GLS was measured as an average of the 18 LV segments. For LAs, the LA endocardium was manually traced at end-systole in the apical 4- and 2-chamber views and LA reservoir strain was evaluated using R-to-R gating.

Intra- and inter-observer variability were assessed by repeating LV GLS and LA reservoir strain assessment in 10 randomly selected patients from the cohort >4 weeks 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 using the logarithmic method.

2.3. Statistical analysis

Categorical variables were presented as numbers and percentages. A Shapiro-Wilk test was performed to evaluate the distribution of the continuous variables, expressed as mean \pm standard deviation or interquartile range (Q1–Q3) as appropriate. A Kruskal-Wallis H test was conducted to determine if there were significant differences in continuous variables between the three groups, and the Mann-Whitney U test was used for comparison between two groups. All analyses were performed using SPSS 22.0 (SPSS Inc, Chicago, IL).

3. Results

3.1. Baseline characteristics

A total of 90 patients (30 controls, 30 cryptogenic stroke patients and 30 patients with paroxysmal AF) were compared (mean age 41.0 ± 11.0 years; 57.8% male). The mean body mass index (BMI) of the study population was 28.6 ± 6.2 kg/m². There were no significant differences in age or BMI between groups. There were no significant differences between groups with regards to baseline cardiovascular risk factors given the exclusionary criteria for the study.

3.2. Echocardiographic parameters

No significant differences were observed in LV parameters between controls and young patients with cryptogenic stroke, including measures of LV size and function. Though there were no significant differences in measures of LA size (LA volume indexed; $p = 0.779$), a reduction in LA function was appreciated in stroke patients relative to the healthy controls, as reflected by a lower LA emptying fraction ($p = 0.009$), LA expansion index ($p = 0.009$) and LA GLS ($p = 0.008$) (Fig. 1).

On evaluation of the three cohorts, a stepwise reduction in functional parameters of the left atrium was appreciated (Table 1) including a reduction in LAEF ($p < 0.01$), LA expansion index ($p < 0.01$) and LA GLS ($p < 0.01$) (Table 1). LAVI was not measurably different between the controls and stroke patients but was significantly larger in patients with paroxysmal AF. Of interest, similar trends were not observed with systolic and diastolic parameters of the left ventricle.

For the LA GLS measurements, the interclass correlation was 0.97 with a 95% Confidence Interval of 0.90–0.99 and the coefficient of variation was 3.42 with a 95% Confidence Interval of 1.67–5.19.

4. Discussion

Our study findings show a reduction in LA functional metrics between a healthy cohort and young cryptogenic stroke population, despite similar age, comorbidities and traditional echocardiographic profiles within groups. When compared to a comparator group with diagnosed young paroxysmal AF and a CHA₂DS₂-VA score of 0, a further reduction in measures of LA function and changes to atrial structure was appreciated. This would indicate that there are early subclinical changes to the left atrium in some

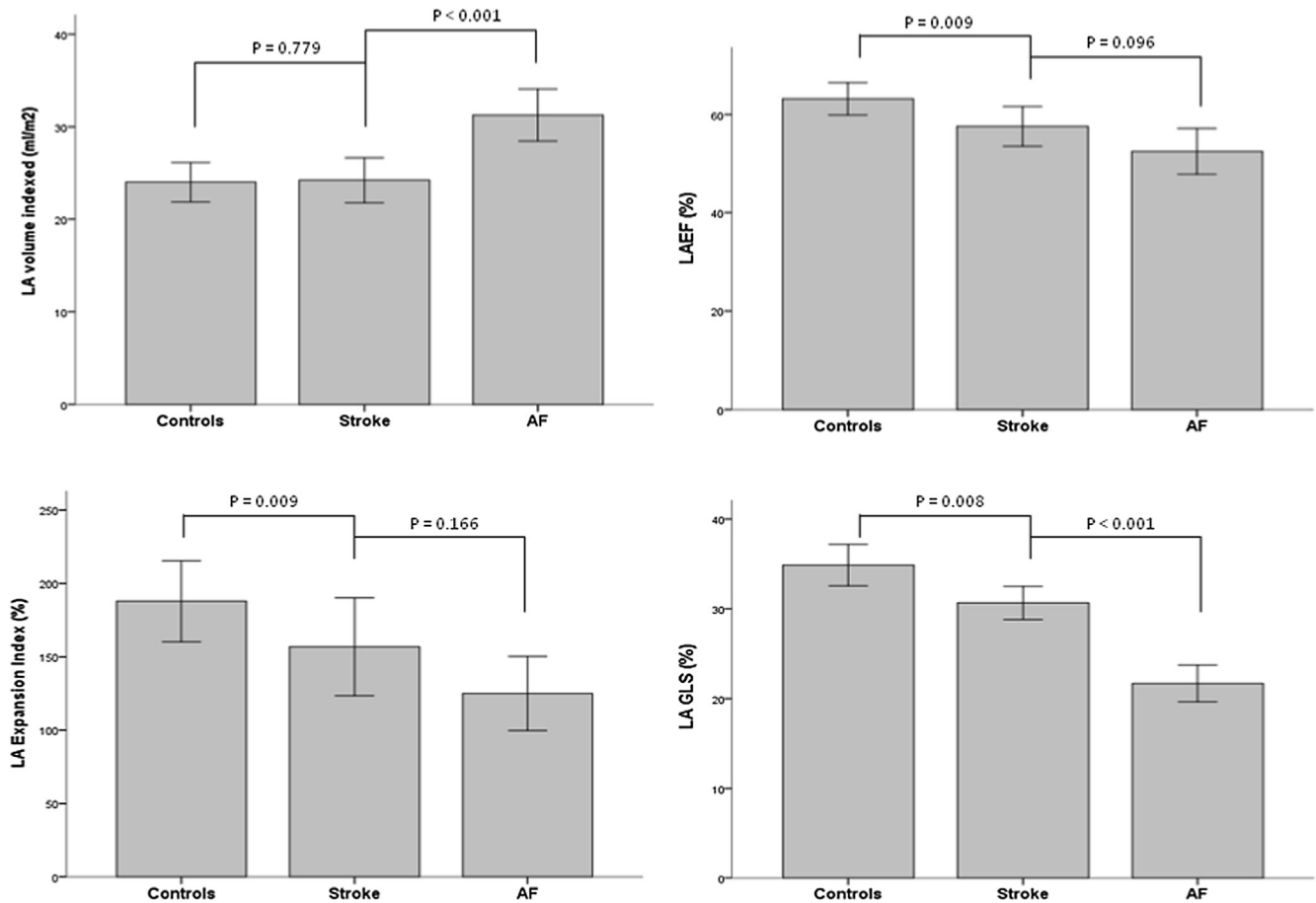


Fig. 1. Comparison of LA parameters between young healthy controls, young cryptogenic stroke and young paroxysmal AF. * Data are expressed as median and interquartile range Error bars: 95% CI.

Table 1

Comparison of echocardiographic parameters between young healthy controls, young cryptogenic stroke and young paroxysmal AF.

Variables*	Controls	Stroke	AF	p Value [†]
LVEDD (cm)	4.7 [4.1/4.9]	4.9 [4.4/5.3]	4.5 [4.3/5.0]	0.269
LVEDD (cm)	2.9 [2.7/3.2]	3.0 [2.6/3.4]	2.9 [2.7/3.1]	0.861
LVEF (%)	63 [58/66]	59 [58/64]	63 [61/69]	0.065
LV GLS (%)	18.7 [16.9/21.4]	17.9 [16.5/19.5]	20.9 [19.4/22.5]	0.983
LV mass (g/m ²)	68 [56/81]	72 [65/85]	75 [62/86]	0.938
E/e' ratio	6.4 [5.3/9.3]	6.7 [5.3/8.6]	6.8 [5.2/9.0]	0.872
RV S' vel (cm/s)	12.8 [11.1/14.3]	12.4 [11.4/13.8]	12.0 [11.0/14.0]	0.421
TAPSE (cm)	2.4 [2.2/2.5]	2.5 [2.0/2.8]	2.6 [2.1/2.8]	0.601
RVSP (mmHg)	23 [20/26]	20 [17/22]	28 [21/29]	0.033
RA area (cm ²)	13 [11/16]	14 [13/17]	16 [14/19]	0.046
LA parameters				
LA max volume (ml/m ²)	24 [19/28]	24 [18/29]	31 [26/34]	<0.001
LA min volume (ml/m ²)	9 [7/11]	10 [7/12]	13 [12/16]	<0.001
LA EF (%)	62 [58/69]	55 [50/63]	52 [46/61]	0.001
LA expansion index (%)	164 [139/222]	122 [101/174]	108 [84/156]	0.001
LA GLS (%)	33 [32/39]	31 [27/34]	21 [19/22]	<0.001

* Data are expressed as the median [interquartile range].

† Kruskal Wallis Test was used to compare the 3 groups.

of the young cryptogenic stroke population without primary causative factors. The changes may originate in the left atrium itself, which contribute to LA remodelling and risk of AF development.

Our findings are in keeping with other studies, which have demonstrated a relationship between markers of atrial pathology and ischaemic stroke development in the absence of captured AF, suggesting that tissue substrate rather than arrhythmia status is the primary driver of stroke risk. Atrial arrhythmias besides AF

have been associated with stroke, with studies showing a relationship between atrial ectopy and paroxysmal supraventricular tachycardia with ischaemic stroke independently of AF [13–15]. Structural changes to the left atrium have also been associated with increased ischaemic stroke risk in the absence of AF; the P-wave terminal force on electrocardiogram, a marker of LA pathology and fibrosis, has been associated with incident ischaemic stroke development [16–18]. Similarly, LA size as quantified by

echocardiography has shown an associated with ischaemic stroke, even after adjusting for AF presence [8,19,20].

Of note, in our study unlike the young paroxysmal AF group, patients with cryptogenic ischaemic stroke had no significant change in LA volume when compared to healthy controls. This would indicate that functional impairment precedes structural changes to the left atrium in this population. As enlargement of the left atrium is a reflection of chronic elevation of LA pressures as well as remodelling from AF, LA function is a sensitive marker of early changes in the atrium and useful in a relatively healthy cohort without traditional cardiovascular risk factors.

Our study had a modest sample size given stringent inclusion criterion and included only young patients with no pre-existent cardiovascular disease or traditional risk factors and were considered low cardiovascular risk. Future studies with larger sample sizes are required to better define the associations found in our study.

5. Conclusion

LA functional parameters were impaired in patients with cryptogenic stroke compared with healthy controls with similar LA volumes. In a young cryptogenic stroke population, a reduction in LA function may provide additional insights in the pathophysiology of stroke.

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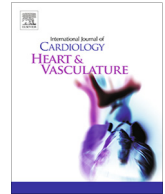
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Update

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Erratum

Erratum regarding missing Declaration of Competing Interest statements in previously published articles



Declaration of Competing Interest statements were not included in the published version of the following articles that appeared in previous issues of IJC Heart & Vasculature

The appropriate Declaration/Competing Interest statements, provided by the Authors, are included below.

1. Impairment of left atrial function and cryptogenic stroke: Potential insights in the pathophysiology of stroke in the young [IJC Heart & Vasculature 26 (2020) 100454] <https://doi.org/10.1016/j.ijcha.2019.100454>

Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

2. Low-frequency and low-intensity ultrasound increases cardiac parasympathetic neural activity and decreases clinic hypertension in elderly hypertensive subjects with type 2 diabetes [IJC Heart & Vasculature 19 (2018) 34–36] <https://doi.org/10.1016/j.ijcha.2018.04.002>

Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

3. The sternal wire code; Solving the problem of missing coronary artery bypass graft records during cardiac catheterization [IJC Heart & Vasculature 19 (2018) 37–40] <https://doi.org/10.1016/j.ijcha.2018.04.004>

Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

4. Hypertrophic cardiomyopathy [IJC Heart & Vasculature 27 (2020) 100503] <https://doi.org/10.1016/j.ijcha.2020.100503>

Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

5. Short term outcome following acute phase switch among P2Y12 inhibitors in patients presenting with acute coronary syndrome treated with PCI: A systematic review and meta-analysis including 22,500 patients from 14 studies [IJC Heart & Vasculature 22 (2019) 39–45] <https://doi.org/10.1016/j.ijcha.2018.11.008>

Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

6. Reverse remodeling in Dilated Cardiomyopathy: Insights and future perspectives [IJC Heart & Vasculature 18 (2018) 52–57] <https://doi.org/10.1016/j.ijcha.2018.02.005>

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7. Mobilization of progenitor cells and assessment of vessel healing after second generation drug-eluting stenting by optical coherence tomography [IJC Heart & Vasculature 18 (2018) 17–24] <https://doi.org/10.1016/j.ijcha.2017.12.003>

Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

8. Trimethylamine N-oxide in atrial fibrillation progression [IJC Heart & Vasculature 29 (2020) 100554] <https://doi.org/10.1016/j.ijcha.2020.100554>

Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

9. Computed tomography guided sizing for transcatheter pulmonary valve replacement [IJC Heart & Vasculature 29 (2020) 100523] <https://doi.org/10.1016/j.ijcha.2020.100523>

Declaration of competing interest: Dr Vaikom S Mahadevan is a principle investigator for pulmonic valve clinical trials for Edwards Life Sciences. No conflicts of interests for any of the other authors.

10. Does combination therapy work in chronic thromboembolic pulmonary hypertension? [IJC Heart & Vasculature 29 (2020) 100544] <https://doi.org/10.1016/j.ijcha.2020.100544>

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11. Vernakalant and electrical cardioversion for AF – Safe and effective [IJC Heart & Vasculature 24 (2019) 100398] <https://doi.org/10.1016/j.ijcha.2019.100398>

Declaration of competing interest: No study specific funding was obtained; however some patients simultaneously participated in an ongoing post approval safety study (SPECTRUM) sponsored by Cardiome Pharma Corp. or were included in a RCT receiving limited grants by the Jubilaeumsfonds of the Austrian National Bank.

12. Not typical angina and mortality in women with obstructive coronary artery disease: Results from the Women's Ischemic Syndrome Evaluation study (WISE) [IJC Heart & Vasculature 27 (2020) 100502] <https://doi.org/10.1016/j.ijcha.2020.100502>

Declaration of competing interest: The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: I, Dr. C. Noel Bairey Merz, serve as Board of Director for iRhythm, fees paid through CSMC from Abbott Diagnostics and Sanofi.