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The Importance of Left Atrial Volume Assessment in Identifying the Cause of Ischemic Stroke

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Abstract

Separating cardioembolic from large artery stroke has important treatment implications. We investigated whether echocardiography could improve Cardioembolic Stroke (CES) prediction compared with traditional measures and cholesterol biomarkers.

Data from 40 consecutive patients presenting with acute ischemic stroke which included brain and carotid imaging, ECG, echo, serum cholesterol and apolipoproteins were independently reviewed. Patients were classified into two groups: a) CES, defined by sustained or paroxysmal atrial fibrillation and <50% stenosis of a perfusing cerebral artery; b) Large artery stroke (LAS) defined as > 50% stenosis of an ipsilateral perfusing cerebral artery, with no evidence of AF on monitoring or evidence of small artery disease on neuroimaging and confirmed by an independent neurologist.

Other than the CES group being older, the baseline characteristics of the two groups were similar. Left Atrial Volume (indexed for body surface area, LAVi) was significantly larger in CES (57.9 +/- 19.4 vs 31.1 +/- 8.3ml/m^2, p<0.01), with a simple equation that utilised age, LAVi and E wave accurately predicting 90% of CES. The difference in LAVi for CES was beyond that anticipated from the presence of AF alone. No differences in any of the lipid biomarkers were observed.

These finding indicate that LAVi is the most important predictor of CES due to atrial fibrillation and is highly predictive of patients with CES due to atrial fibrillation. Cholesterol biomarkers offered no additional discriminatory value.

Keywords: Atrial fibrillation; Apolipoproteins; Diagnostic techniques and procedures; Echocardiography; Ischemia; Stroke

Introduction

As stroke is a heterogeneous disease there is a pressing need for accurate and early determination of stroke subtype [1] as this can have significant impact on patient management [2] and outcomes [3].

Cardioembolic cerebral infarction accounts for 30% [4] of all cerebral infarcts and often result in poor patient outcomes including increased risk of recurrence and early mortality [5]. Although the emboli may originate from multiple cardiac sources [6], atrial fibrillation is considered the most likely primary risk factor [4].

While echocardiography has been recommended to help determine the cardioembolic source of stroke and to inform primary and secondary prevention strategies of a secondary stroke [6], the diagnosis of Cardioembolic Stroke (CES) is often inferential; based on supportive historical data, neuroimaging, and less often, the identification of a cardiac source for the patient [7].

Earlier studies have demonstrated an association between left atrial size and ischaemic stroke [8], even in patients without atrial fibrillation [9]. More recent studies have extended this observation to cardioembolic and other stroke sub-types [10-12].

To date however, no studies have investigated degree of left atrial enlargement as a predictor of cardioembolic stroke in patients with atrial fibrillation, and the potential of using left atrial volume to differentiate CES from other forms of stroke.

The purpose of this study is to determine whether echocardiographic parameters can be used to differentiate CES from those due to atherosclerotic emboli of a large artery.

Methods

Adult patients presenting to a district hospital in Perth, Western Australia with an acute ischaemic stroke within 48 hours of symptom onset were identified using full clinical history, neurological examination and laboratory analyses, lipid profile including apolipoproteins (ApoA1, ApoB, and Lp (a)), and an Electrocardiogram (ECG). Baseline Brain Computed Tomography (CT) was performed for each patient. 24-48 hour ambulatory ECG monitoring (Holter monitor) was performed if Atrial Fibrillation (AF) was not present on a resting Electrocardiogram (ECG). Cervical artery imaging (carotid ultrasound, CT angiography or time of flight MR Angiography) was performed for all patients. Follow-up neuroimaging (brain CT or MRI) was performed as clinically indicated.

Brain CT, MRI and cervical artery imaging were reviewed by an independent neurologist (DJB) and patients were classified as Large Artery Stroke (LAS) or presumed CES. Patients who potentially had other forms of stroke where excluded from this study. The neurologist was blinded to the presence or absence of atrial fibrillation, the echo findings and the laboratory analyses.

Full transthoracic echo (TTE) was performed in all patients in a single laboratory using standard criteria [13]. Left Atrial Volume (LAV) was assessed using the recommended criteria [14], and indexed for body surface area (LAVi). Mitral inflow E wave velocity, E:E', left ventricular mass index and pulmonary artery systolic pressure were all calculated using published criteria [15]. In the setting of atrial fibrillation, the mitral A wave was absent, and E wave and E' velocities were only measured if felt clinically appropriate.

Patients were classified into one of two groups: a) CES, defined by the presence of sustained or paroxysmal atrial fibrillation and less than 50% stenosis in an artery supplying the region of stroke, or b) LAS defined by atherosclerosis of an artery supplying the region of stroke, with no evidence of AF or small artery disease on neuroimaging.

The data were analysed using SPSS statistics version 22. Categorical variables were summarized as percentages while continuous variables were expressed as means and standard deviations. Differences were determined using the Chi-square statistic and Fishers Exact Test for categorical variables or t-test for continuous variables. The contribution of various atrial measures against LAVi was determined by ANOVA with comparison of F scores and their probabilities. Associations between stroke type and other variables were assessed using multiple logistic regression modelling. Receiver operating characteristics curves were constructed to assess discrimination between CES and LAS using STATA version 13.

This project followed the ethical guidelines set out by the National Health and Medical Research Council of Australia, and received approval from by the Human Research Ethics Committees (HREC) of Sir Charles Gairdner Hospital and The University of Notre Dame of Australia.

Results

40 patients with definite ischaemic strokes were included; 20 with LAS and 20 with CES. Clinical classification, performed at the time of the stroke, was completely concordant with the independent neurologist review.

For the entire group, the mean age was 70 ±13.5 years 25 (63%) were male, 22 (55%) were current or previous smokers, 30 (75%) had hypertension and 12 (30%) had diabetes mellitus. The baseline clinical characteristics of the two groups were similar except for the CES group being older (77 vs 64 years, $p<0.001$) and more likely to be on antihypertensive medication (95% vs 65%, $p<0.001$) than patients in the LAS group (Table 1). The most commonly prescribed antihypertensive medication was a renin-angiotensin blocking agent. All patients with CES were noted to have atrial fibrillation during their hospital admission, whereas no patients with LAS had atrial fibrillation during their admission or on subsequent continuous ECG monitoring.

Variable	LAS	CES	p-value
Age in years, mean (SD)+/- SD)	63.7 (13.4)	77.4 (7.1)	<0.001*
Male, n (%)	14 (70%)	11 (55%)	0.51
SBP at stroke, mean (SD)	152 (15)	152 (21)	0.93
Comorbidities, n (%)			
Diabetes mellitus	6 (30%)	6 (30%)	1.00
Hypertension	16 (80%)	14 (70%)	0.72
Prior IHD diagnosis	6 (30%)	11 (55%)	0.20
GFR < 60ml/min	4 (20%)	8 (40%)	0.30
Risk behaviours, n (%)			
Smoking status	9 (45%)	2 (10%)	0.06
Alcohol Consumption	11 (55%)	8 (40%)	0.19
Medications prior to stroke, n (%)			
Antiplatelets	10 (50%)	16 (80%)	0.10
Anticoagulants	2 (10%)	1 (5%)	1.00
Statin therapy	8 (40%)	9 (45%)	1.00
Antihypertensive therapy	13 (65%)	19 (95%)	0.04*
Lipid biomarkers, mean (SD)			
Total cholesterol	3.95 (1.17)	3.70 (1.08)	0.50
LDL	2.47 (0.82)	2.36 (0.95)	0.68
HDL	1.07 (0.29)	1.16 (0.42)	0.46
Triglycerides	1.96 (1.57)	1.33 (0.61)	0.10
APO A1	1.20 (0.25)	1.21 (0.28)	0.98
APO B100	0.81 (0.29)	0.76 (0.26)	0.54
Lp (a)	0.33 (0.38)	0.38 (0.43)	0.66
Data are presented as mean (SD) or as the number, n (%). P-values were calculated using independent samples t-test or Fishers Exact Test for continuous and categorical variables respectively. SBP: Systolic Blood Pressure; GFR: Glomerular Filtration Rate; IHD: Ischaemic Heart Disease; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein, APO A1: Apolipoprotein A1; APO B100: Apolipoprotein B100; Lp (a): Lipoprotein (a). * P<0.05 for difference between groups by t-test or Fishers Exact test as appropriate.			

Table 1: Clinical characteristics: Large Artery Stroke (LAS) vs Cardioembolic (CES).

Lipid and Lipoprotein Profiles

No significant difference in any of the measured lipids, lipoproteins or apolipoproteins was identified between the two groups (Table 1).

Echocardiography

The indexed LAV (LAVi) was significantly larger in those with CES compared with LAS (CES 57.9 ± 19.4 ml/m^2 v LAS 31.0 ± 8.3 ml/m^2, p<0.001, Figure 1).

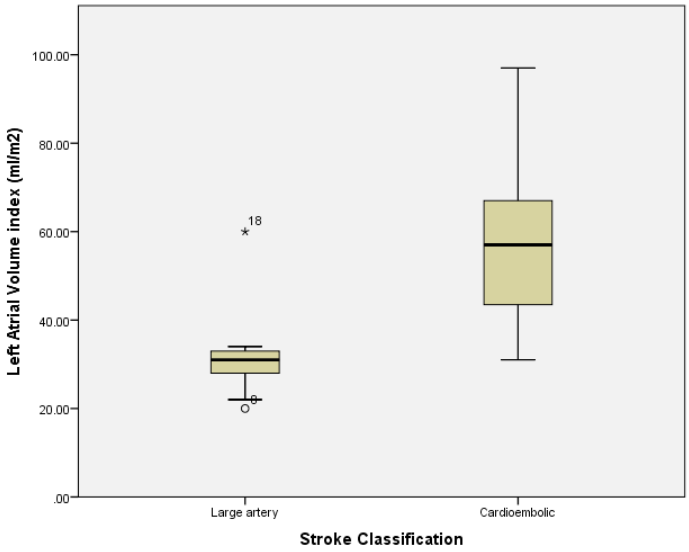

Figure 1: Box plots of LAVi by stroke type. The line inside each box represents the median, the upper and lower limits of the boxes represent the 25th and 75th percentiles respectively with the bars representing the 10% and 90% range. Points outside this range are shown as 'o' and '*'.

The ejection fraction was similar between groups (64 ± 10% vs 57 ± 17%, p=0.3). To identify the cause for left atrial enlargement, LV mass, diastolic function and valvular abnormalities were evaluated. Left ventricular mass was significantly higher in those with CES compared with their large artery counterparts (118 ± 40 g/m^2 vs 87 ± 30 g/m^2, p=0.02).

There were significant differences in diastolic function between the two groups. Mitral inflow E waves were higher in CES (104 ± 29 ml/m^2 vs 72 ± 20 ml/m^2, p<0.001), and the medial mitral annular descent velocities (E') were numerically but not significantly lower (6.1 ± 2.0 cm/s vs 7.2 ± 2.2 cm/s, p=0.2), which may be due to the low numbers of E' measurements performed in the setting of atrial fibrillation (27 E' measurements performed). The ratio of E:E' as a marker of LV filling pressures, was higher in the CES group (18.8 ± 8.3 vs 10.6 ± 2.9, p=0.004). Measures of diastolic function associated with LAVi were left ventricular mass (F=3.27, p=0.04) and E:E' ratio (F=3.6, p=0.03), with E wave and septal E' velocity not being significantly different. E:A ratio could not be compared because of the absence of a mitral inflow A wave velocity in atrial fibrillation. The estimated Pulmonary Artery Systolic Pressure (PASP) was numerically but not statistically different, measuring 42.8 ± 13.4 mmHg in the cardioembolic group and 32.5 ± 2.12 mmHg in the large artery group. Accurate data on PASP was only available in 14 patients (41%) due to insufficient tricuspid regurgitation in the remainder.

Mitral valve disease was more common in patients with CES with 50% of patients having mild or moderate mitral regurgitation compared with only a single patient in the LAS group (p<0.001). No patients had severe mitral regurgitation. Despite trends toward more significant aortic valve disease in the cardioembolic group, these were not significant (Table 2).

Parameter	LAS	CES	p-value
TTE measure, mean (SD)			
LA volume index (ml/m^2)	31.1 (8.3)	57.9 (19.4)	<0.001*
LV mass index (g/m^2)	87.4 (29.6)	118.3 (40.2)	0.02*
LV diastolic diameter (cm)	4.69 (0.68)	4.72 (0.95)	0.02*
Ejection Fraction (%)	63.7 (9.7)	57.4 (17.1)	0.92
E wave (cm/s)	71.6 (20.0)	103.5 (28.6)	0.001*
E' velocity (cm/s)	7.2 (2.2)	6.1 (2.0)	0.23
E:E'	10.6 (2.9)	18.8 (8.4)	0.006*
PASP (mmHg)	32.5 (2.12)	42.8 (13.4)	0.31
Valvular disease			
Mild or moderate MR, n (%)	1 (5%)	10 (50%)	0.001*
Mild MS, n (%)	0 (0%)	1 (5%)	0.49
Mild AR, n (%)	0 (0%)	3 (17%)	0.23
Mild AS, n (%)	7 (35%)	2 (10%)	0.12
Severe AS, n (%)	0 (0%)	3 (15%)	0.23

LV: Left Ventricle; LA: Left Atrium; PASP: Estimated Pulmonary Artery Systolic Pressure. For valvular disease, MR: Mitral Regurgitation; MS: Mitral Stenosis; AR: Aortic Regurgitation; AS: Aortic Stenosis. No patients in our cohort had greater than moderate MR or MS, and no patients had moderate or greater AR. No LAS patients had moderate AS. *P<0.05 for difference between groups by t-test or Fishers Exact test as appropriate.

Table 2: Echocardiography parameters: Large Artery Stroke (LAS) vs Cardioembolic Stroke (CES).

Predicting Cause of Stroke

Logistic regression was used to determine the contribution of several variables in predicting stroke type. Various models were constructed using the available cardiac parameters produced by TTE. The model developed using both LAVi (p=0.05) and E wave (p=0.55) resulted in the greatest Pseudo R^2 and area under the ROC curve (AUC) estimates (65.7% and 96.1% respectively). Age at stroke was kept in the model (p=0.16) as it was considered an important clinical determinant and had minimal impact on the model's R^2 and AUC values (Table 3). Model 2, utilising only age and LAVi, was also significant (p=0.015) but with lower with Pseudo R^2 (56.4%) and ROC area under the curve values (93.8%, Table 4, Figure 2). Similar modelling based on E wave was not significant.

Variable	Coefficient	SE	p-value	Odds ratio (95% CI)
Model 1 (n=30)				
Age at stroke (years)	0.1576	0.1111	0.156	1.17 (0.94–1.46)
LA volume index (ml/m^2)	0.1313	0.0671	0.050*	1.14 (1.00–1.30)
E wave (cm/s)	0.0645	0.0336	0.055	1.07 (1.00–1.14)
Model 2 (n=34)				
Age at stroke (years)	0.1095	0.0641	0.088	1.12 (0.98–1.27)
LA volume index (ml/m^2)	0.1237	0.0508	0.015*	1.13 (1.02–1.25)
Logistic regression model based on 30 observations with for predicting stroke type. Pseudo R^2 and ROC area under the curve were 65.7% and 96.1% for Model 1; and 56.4% and 93.8% for Model 2. *P<0.05.				

Table 3: Multiple logistic regression model for the prediction of cardioembolic stroke.

Model	AUC	Optimal Cut-off	Sensitivity	Specificity	Correctly classified
Model 1 (n=30)	0.961 (0.900-1.021)	0.57	86.7%	93.3%	90.0%
Model 2 (n=34)	0.938 (0.866-1.00)	0.68	75.0%	94.4%	85.3%
Model 1 is a predictive model based on age, LAVi and E wave measurements while Model 2 is based only on age and LAVi. AUC = ROC area under the curve.					

Table 4: Diagnostic properties of predictive models.

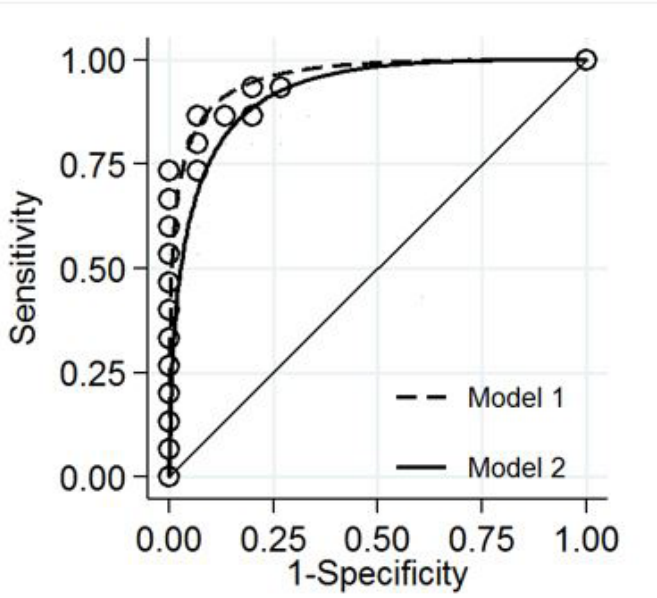

Figure 2: ROC plot of sensitivity and specificity for the stroke prediction model. Receiver operating characteristic (ROC) curves for Model 1 and 2 discriminations of CES from LAS. Dots represent points from Model 1. Statistical comparison of the AUC of both models by Chi2 shows no significant differences (p=0.327).

The equation from the modelling that yielded the best predictor of CES was:

Model 1: (86.7% sensitivity and 93% specificity at probability cut-off 0.57): CardioEm = exp(-22.6454 + 0.1576 * Age + 0.1313 * LAVi + 0.0645 * Ewave) Probability, p(CardioEM) = (CardioEm / (1 + CardioEm) If p(CardioEm >= 0.50 then the patient is likely to have had CES

Discussion

This study demonstrated that, in patients with atrial fibrillation on presentation with ischaemic stroke, LAVi was the single most important predictor of CES with abnormal diastolic function appearing to be the primary driver of left atrial enlargement. Age was not a significant risk factor for stroke after correction for LAVi. No lipid biomarker, alone or in combination, was useful to separate CES from LAS, and therefore cannot be recommended as a diagnostic tool. Similarly, presentation blood pressure was not useful as a discriminator. The clinical classification of patients into CES and LAS was confirmed via independent neurological review, blinded to the echo and ECG findings, further strengthening our result.

Left Atrial Volume and Stroke

LAVi was significantly higher in the CES group, with the driver for increased LAV appearing to be abnormal diastolic function with increased filling pressures. Mitral E wave velocity, a measure of early diastolic filling, was higher in the cardioembolic group, as was the E:E', a marker of left ventricular filling. In atrial fibrillation, the E wave velocity may increase in the absence of an A wave. However, multivariate analysis revealed a 14% increase in CES risk for every unit increase in LAVi even after controlling for age and E Wave velocity.

LAV is considered a marker of chronically increased left atrial pressure [16], and a large left atrium is associated with atrial fibrillation [17,18]. Possible causes for left atrial enlargement include valvular disease and diastolic dysfunction [19]. Left ventricular systolic dysfunction has also been associated with ischemic stroke [20]. The CES group had a higher LV mass than those in the LAS group (Table 2) despite similar blood pressures on presentation. A greater proportion of patients in the CES group were receiving antihypertensive therapy than those in the LAS group, consistent with hypertension being more prevalent in the CES group. We found a higher E:E' ratio in the CES group but similar E' velocities (Table 2), suggesting that that the E wave velocity was the predominant driver for the higher E:E' ratio in the CES group. It is possible the increased E wave velocity was due to atrial fibrillation itself (and the absence of an atrial contraction wave) rather than diastolic dysfunction, but the increased left atrial volume, increased left ventricular mass and higher pulmonary artery pressures suggest possible diastolic dysfunction. In the setting of left ventricular hypertrophy and diastolic dysfunction, atrial fibrillation is likely to have developed as a result of these primary abnormalities.

Atrial fibrillation is known to induce left atrial remodelling and atrial enlargement [21], particularly with chronic atrial fibrillation. However, the difference in left atrial volume in our two groups was large (26.8 ml/m^2) and beyond that described where the arrhythmia appears to be the only driver [22]. There appear to be other additional drivers of increased left atrial volume at play, such as abnormal diastolic filling parameters as described above.

Mitral regurgitation, which can cause left atrial enlargement and atrial fibrillation, is commonly found in patients with CES [23]. We found that half of the patients with CES had mild or moderate mitral regurgitation, compared with only 1 patient in the LAS group. We did not explore this possible association further because of small numbers.

Another study found LAV was an independent predictor of first ischemic stroke in patients without documented atrial fibrillation [24]. The Framingham heart study found that an enlarged LAV was associated with increased stroke incidence even when adjusted for age, hypertension, left ventricular hypertrophy and prevalent atrial fibrillation. However, neither of these studies examined LAVs in differing causes of stroke. The paroxysmal nature of some atrial

fibrillation makes it difficult for echo follow-up studies to rule out the disease, particularly if it develops after the initial echo study was performed. We note another study examined whether echocardiography can predict Paroxysmal Atrial Fibrillation (PAF) as diagnosed by 7-day Holter monitoring, in patients with cerebral ischemia presenting in sinus rhythm. These authors concluded that the ratio of indexed LAV to an E:A wave ratio <2.3 can effectively rule out paroxysmal atrial fibrillation [25]. We did not examine this association, since patients in the CES group in our study had confirmed persistent AF and no A-wave was present on echo.

However, other studies have recently reported changes in LAVi by stroke sub-types, with patients with CES being significantly higher than other forms of ischaemic stroke [11,12,26]. While differences in patient classification and study design make direct comparison between these and our own study difficult, collectively they demonstrate the value of using LAVi to identify CES patients as part of the clinical decision to utilise anticoagulants. While, like Shaikh et al. we noted the risk of CES increased with a LAVi ≥ 34 ml/m^2, our study also demonstrated improved discrimination between LAS and CES patients could be achieved by also utilising the patient's E wave measurements. Introduction of other electrocardiographic measures into the model failed to improve the discernment of the stroke types but this needs to be further investigated in a larger sample of patients.

Age and Stroke

Age, which is a known predictor of atrial fibrillation, was significantly greater in the CES group, a finding that is consistent with previous studies [27,28]. However, we found that age no longer remained a significant predictor of CES when corrected for atrial volume, a finding consistent with the work of Abhayaratna et al. [29].

Cholesterol Biomarkers and Stroke

Several studies have previously demonstrated associations between lipid and apolipoprotein abnormalities and ischemic stroke but may [30] or may not have separated subjects by ischaemic stroke subgroups [31]. As our study did not have a control group, we cannot comment on changes in lipid biomarker levels and ischaemic stroke relative to a reference group, however we found no differences in lipid and lipoprotein levels between the two ischaemic stroke sub-types suggesting a similar metabolic profile and that other parameters may be more useful to separate these two groups.

Study Strengths and Limitations

Our study has several strengths; our patients were extensively investigated, and the cause of stroke carefully characterized, and blinded assessment confirmed our allocation into the two groups (small vessel strokes were excluded from the study). This has allowed a small sample size to report significant differences. Secondly, all patients had a detailed echocardiographic evaluation by a single experienced provider allowing for novel aspects of echocardiography and stroke to be evaluated.

In our study, patients were defined as being cardioembolic if atrial fibrillation was identified and was confirmed by a blinded classification based on neuro-imaging without reference to cardiac rhythm. This complete concordance strengthens our assumption that the left atrium was the source of a cerebral embolus, and was caused by the presence of atrial fibrillation. This also decreased the potential that subclinical paroxysmal atrial fibrillation was present in patients with large artery disease.

Our study did not rigorously examine the mechanism of development of atrial fibrillation. The higher E:E' ratio in the CES group, but similar E' velocities, was due predominantly to higher E wave velocities. It is possible the increased E wave velocity was due to atrial fibrillation rather than diastolic dysfunction, but the increased left atrial volume, increased left ventricular mass and higher pulmonary artery pressures suggest possible diastolic dysfunction. Our study also did not examine patients with occasional paroxysmal atrial fibrillation, since all of our patients had persistent atrial fibrillation demonstrated on ECG as part of their stroke workup, although recent work is noted [32]. Irrespective of the underlying cause of atrial fibrillation, our study has demonstrated the importance of left atrial volume in cardioembolic stroke.

Although a larger study size may have identified some differences in biomarkers between groups, the strength of association between LAVi and stroke type in our study suggests this measure is of greater importance. Our study excluded patients with small vessel disease and stroke of uncertain cause so replication of our findings in these populations is required. No patients had alternative cardiac sources of embolism (e.g. left ventricular thrombus or atrial myxoma), and we acknowledge that atrial volume may not predict CES if an alternative cardiac source of embolism is present.

In our study, patients with CES were all demonstrated to have atrial fibrillation whereas patients with LAS were all demonstrated to have sinus rhythm including during extended testing. An independent neurologist unaware of the patient's rhythm status independently verified the allocation of patients to CES and LAS groups. We have not prospectively applied our algorithm to patients who presented with CES but were in sinus rhythm on arrival. This would require separate study to fully validate our algorithm.

Finally, not every measure was performed in every patient. The E', for example, was only measured in 15 patients with LAS and 12 with CES (due to the presence of atrial fibrillation), which may explain some non-significant results. Similar problems were

encountered with estimation of the pulmonary artery systolic pressure. A larger sample size would help to address this concern.

Conclusions

Left atrial volume indexed for body surface area is the most important predictor of CES due to atrial fibrillation in our study. A simple equation based on age, LAVi and E Wave was found to be highly predictive of CES due to atrial fibrillation, and there was no additional discriminatory value from lipid and apolipoprotein measurement. A larger sample size, focusing on measures of abnormal myocardial relaxation and filling pressures as predictors of CES, would help clarify the cause for the increase in LAV.

Author Contributions

DP and TB developed the original concept for this study and oversaw the data collection which was largely undertaken by SB. DB assessed the brain CT, MRI and cervical artery images and classified patients as large artery stroke (LAS) or presumed CES. MB was the senior biostatistician involved in the analysis. SB drafted the initial manuscript which was reviewed and updated by JC. All authors critiqued the data analysis, contributed to its interpretation and were involved in drafting the manuscript prior to giving their approval for it to be submitted for review.

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