Ischaemic Stroke and the Echocardiographic "Bubble Study": Are We Screening the Right Patients?

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Background   Patent foramen ovale (PFO) is a potential mechanism for paradoxical embolism in cryptogenic ischaemic stroke or transient ischaemic attack (TIA). PFO is typically demonstrated with agitated saline ("bubble study", BS) during echocardiography. We hypothesised that the BS is frequently requested in patients that have a readily identifiable cause of stroke, that any PFO detected is likely incidental, and its detection often does not alter management.

Methods   This was a retrospective observational study of patients with recent ischaemic stroke/TIA referred for a BS. Patient demographics, stroke risk factors, vascular/cerebral imaging results and transoesophageal echocardiogram (TOE) reports were recorded. A "modified" Risk of Paradoxical Embolism (RoPE) score was calculated. Change in management was defined as antiplatelet/anticoagulant therapy alteration or referral for PFO closure. Bubble Study complications were recorded.

Results   Among 715 patients with ischaemic stroke/TIA referred for a BS, 8.7% had atrial fibrillation and 9.2% had carotid stenosis ≥70%. At least three stroke risk factors were present in 39.3% and only 47.1% of patients screened had a "modified" RoPE score of >5. A PFO was detected in 248 patients of whom only 31% (77/248) had a subsequent change in management. Of BS performed, 1/924 patients (0.1%) suffered a TIA as a complication.

Conclusions   The echocardiographic BS is frequently performed in patients that have a readily identifiable cause of stroke and whose PFO unlikely relates to the stroke/TIA. Bubble Study findings resulted in a change in management in the minority. The procedure is safe but the complication rate warrants informed consent.

Keywords   Patent foramen ovale • Agitated saline testing • Bubble study • Cryptogenic stroke • Ischaemic stroke • RoPE score

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Background

The foramen ovale has a pivotal role in fetal development. It allows oxygenated blood to flow from the right to left atrium, in the absence of blood flow through the fetal lungs. In the majority of people, components of the interatrial septum fuse after birth. In 15-35% of the population however, a small communication may persist, giving rise to a patent foramen ovale (PFO) [1–6]. Cryptogenic ischaemic strokes are ''symptomatic cerebral infarcts for which no probable cause is identified after adequate diagnostic evaluation'' [7]. Cryptogenic stroke may account for up to 40% of ischaemic stroke [8]. Case control studies suggest that PFO is a common cause of cryptogenic stroke (OR for all ages 1.83 [95% CI 1.25–2.66]), likely via a paradoxical (venous to arterial) embolism [9,10].

Patients with a diagnosis of cryptogenic stroke often undergo agitated saline contrast echocardiography, otherwise known as a ''bubble study'' (BS), to assess for the presence of a PFO. The American Society of Echocardiography recommends contrast be ''composed of $\geq$8 mL of bacteriostatic normal saline agitated with 0.5 mL of room air, agitated back and forth between two sterile syringes using a three-way stopcock just before IV bolus injection through a forearm or hand vein'' [11]. A Valsalva manoeuvre or cough may subsequently be used to transiently increase right atrial pressure and thus increase the likelihood of PFO detection by transient reverse shunt. There is some evidence to suggest that agitated saline testing carries a small risk of stroke or transient ischaemic attack (TIA) as a procedural complication [12].

It has been hypothesised that, in those with cryptogenic stroke, adding percutaneous closure of a PFO to antiplatelet therapy may reduce stroke recurrence vs antiplatelet or anticoagulant therapy alone. Initial trials and subsequent meta analyses did not demonstrate a significant benefit, with the exception of the Amplatzer device [13–16]. Three subsequent publications have all reported a statistically significant reduction in recurrent ischaemic stroke following PFO closure [17–19]. This newly proven benefit of closure relates to more stringent patient selection, i.e. referring for closure patients whose PFO is likely causative of the stroke, rather than being an incidental finding. This selection is based on the absence of traditional vascular risk factors (e.g. diabetes mellitus) and the presence of high risk echocardiographic findings (e.g. an aneurysmal septum and a moderate to large interatrial shunt).

The echocardiographic BS is frequently requested following ischaemic stroke, and is likely to be increasingly requested, given the favourable results of the aforementioned recent publications of PFO closure. However, the clinical utility of more widespread referral for a BS in the diagnostic work-up of patients with ischaemic stroke in routine clinical practice is uncertain, particularly in view of difficulty attributing the cause of the embolic ischaemic stroke to a detected PFO, the low rate of recurrent stroke of patients with cryptogenic stroke and PFO (about one per 100 person-years), and the substantial cost of uncomplicated PFO closure, estimated to be about $15,000 or higher [20].

We hypothesised that the BS is frequently performed in patients that have a readily identifiable cause of stroke,

Table 1 **Baseline characteristics of stroke patients undergoing a ''bubble study''.**

	Mean	Standard Deviation	Count
Age (years)	54	15	
Sex			
Male			448 (62.7%)
Female			267 (37.3%)
Transoesophageal echocardiography performed			339 (47.4%)
Hypertension			310 (43.3%)
Hypercholesterolaemia			331 (46.3%)
Diabetes			143 (20.0%)
Atrial fibrillation			62 (8.7%)
Smoking history			174 (24.3%)
Carotid stenosis ($\geq$ 70%)			66 (9.2%)
Aortic plaque			203 (28.4%)
Ischaemic heart disease			90 (12.6%)
Brain infarction in multiple arterial territories			214 (29.9%)
Antiplatelet/Anticoagulant Therapy of PFO Patients at Admission			
No antiplatelet			202 (81.5%)
Aspirin			35 (14.1%)
Clopidogrel			4 (1.6%)
Coplavix			3 (1.2%)
Other antiplatelet			4 (1.6%)
Oral anticoagulant			8 (3.2%)

whose PFO unlikely relates to the stroke, and that due to over-screening, the study outcome often does not alter management. We additionally assessed the complication rate of the BS itself.

Methods

A retrospective observational study was performed at Sir Charles Gairdner Hospital and Royal Perth Hospital, two tertiary centres in Western Australia, between October 2003 and January 2016. Using the local echocardiographic image server, a patient list was generated of those who had undergone an agitated saline contrast study. Search terms ''bubble study'' and ''agitated saline test'' were used. This list was used to obtain the relevant discharge summary pertaining to the admission prompting the contrast study.

Baseline demographic data, stroke risk factors (including age ≥ 65 years) (Table 1), medication history and the indication for the echocardiographic contrast study were recorded. We noted indications for the BS as stroke/TIA (ischaemic subtype only) or ''other'', with the latter including referrals to investigate pulmonary hypertension, or peripheral thromboembolism. Patients were excluded if the discharge summary contained inadequate information. Patients who either had a non-stroke indication for the BS, or inadequate information in the discharge letter, were also excluded from further analysis. When assessing for a complication of a BS, however, both the stroke and non-stroke groups were analysed.

For those with a diagnosis of stroke/TIA, we documented the findings of computed tomography (CT) and magnetic resonance imaging (MRI) brain scans, including any angiography studies. Infarcts distributed across more than one major cerebral artery territory were classed as ''multi-territory'' infarcts. To ascertain the proportion of contrast studies performed in all stroke/TIA admissions during the study period, we obtained a list of all admissions with an ICD-10 code for cerebral infarction or TIA (I63.9 and G45.9). We further used the local echocardiogram servers to search for all transthoracic studies performed in the study period using the search terms ''stroke'', ''CVA'' and ''TIA''.

For the purpose of this study, cryptogenic stroke was defined as a ''brain infarction that is not attributable to a source of definite cardioembolism, large artery atherosclerosis, or small artery disease despite a standard vascular, cardiac, and serologic evaluation'' [21]. To assess for large vessel disease in the cohort of patients referred for a BS, we recorded the findings of carotid Doppler studies and CT angiograms of the cranial/extra cranial vessels. In those who underwent transoesophageal echocardiograms and CT angiography, we further noted the presence of aortic plaque.

Kent et al. developed the Risk of Paradoxical Embolism (RoPE) Score in order to assist clinicians in assessing whether a PFO is causative vs incidental in cryptogenic stroke [9]. This index incorporates a number of variables including age, hypertension, diabetes, previous stroke, history of smoking and a cortical infarct on imaging. The RoPE score ranges from 0 to 10 and a higher score (i.e. younger patients with fewer standard risk factors) implies a greater likelihood that the stroke is PFO-related. The presence of a cortical infarct was not recorded in this study. We instead calculated a ''modified'' score, substituting multi-territory infarct with cortical infarct, based on evidence that multiple ischaemic lesions may be more commonly seen in those with a PFO [22,23].

A ''positive'' bubble study was defined as those with identification of a right-left shunt with the appearance of bubbles in the left atrium within three cardiac cycles. All subsequent discharge letters following the BS were reviewed to assess for any procedural complications with a follow-up period until March 2017.

Discharge summaries relating to the index admission which resulted in the BS were used to assess for a change in management as a result of the contrast study. Antiplatelet or anticoagulant therapy prior to and post contrast study were recorded, as well as any referrals for percutaneous closure of a PFO. Consultation letters were obtained for patients that had a change in management or a referral for PFO closure. A ''change in management'' was defined as commencement of antiplatelet or anticoagulant, a change in antiplatelet or anticoagulant, or referral for PFO closure. This change was strictly noted as a result of PFO detection. The local electronic patient management system was used to record insurance status in those with a PFO.

Data analysis was performed using SPSS Statistics Version 21 (IBM, Armonk NY, USA). Baseline characteristics are described as frequencies (%) and means ± SD. The presence of a risk factor was described as categorical variables and all risk factors were summed to create a cumulative risk factor number for each patient. Significant differences between categorical and normally distributed continuous variables were calculated using Fisher's exact test and an independent t-test respectively. To develop an understanding of factors contributing to referral for PFO closure, a multivariate backward entry logistic regression (cut-off p-value = 0.1) was performed on all cardiovascular risk factors, imaging findings and insurance status. Age categories for the logistic regression were defined as (<45, 45–65 and >65 years) with the age group >65 years used as a reference. P values <0.05 are described as significant.

Ethical approval was obtained from both hospitals after registering the study as a Quality Improvement Activity (No. 12442). A consent waiver was granted. Our study was granted permission for publication.

Results

Between October 2003 and January 2016, 9,008 patients were admitted with a cerebral infarct or TIA. 9,438 transthoracic studies were performed for a similar indication during the study period. 924 patients underwent a BS, of whom 715 had a diagnosis of ischaemic stroke/TIA and constitute the study cohort. The remaining 209 patients were excluded (Figure 1).

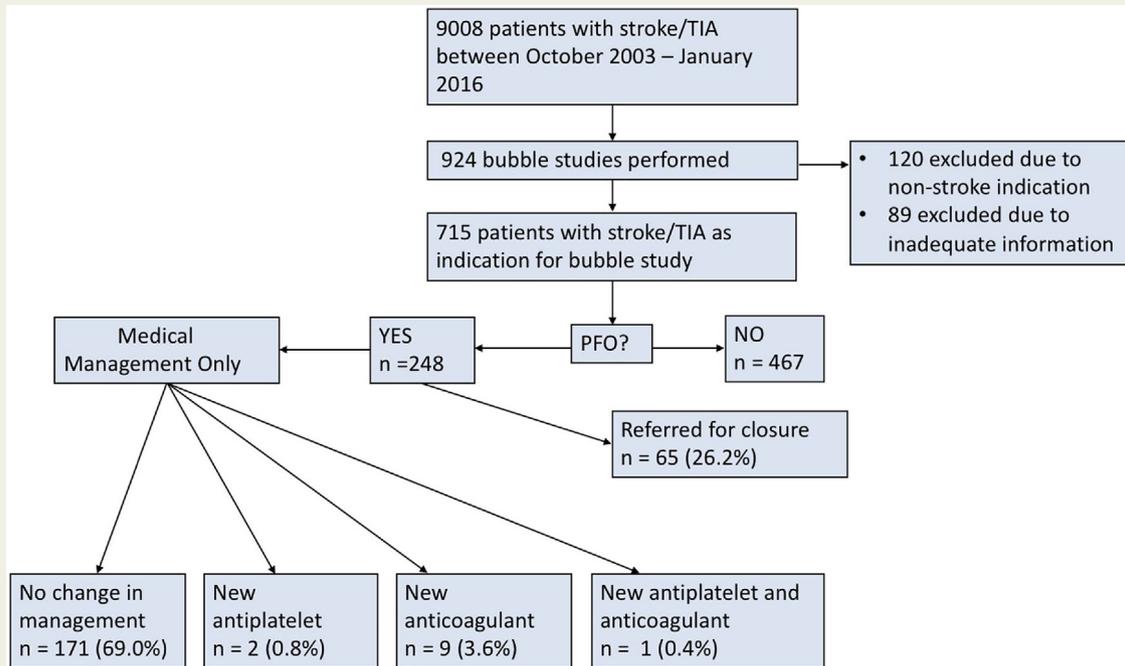Table 1 shows the baseline characteristics of the study cohort. The mean (±SD) age of the ''bubble'' cohort was

Figure 1 Flow chart of the study protocol.
Abbreviations: TIA, transischaemic attack; PFO, patent foramen ovale.

54 ($\pm$15) years and 62.7% (448/715) were male. 248 patients (34.7%) who underwent a BS were aged >60 years.

Among 715 patients with ischaemic stroke/TIA referred for a BS, 39.3% had $\geq$3 conventional stroke risk factors (Figure 2) and 8.7% had atrial fibrillation (diagnosed prior to discharge from hospital). Of the total stroke cohort, 66 patients (9.2%) had carotid stenosis $\geq$70%. Among 663 patients with carotid imaging however, the proportion was 10.0%. Only 47.1% of stroke/TIA patients screened for PFO had a "modified" RoPE score of >5 (Figure 3).

The prevalence of PFO in the total stroke cohort was 34.6%. Among those without stroke risk factors however, the PFO prevalence was 47.8% (63/132). Of patients undergoing a BS for stroke/TIA, 116 patients (16.1%) had no infarct detected on CT/MRI head (however 14 patients had no CT/MRI imaging available for review).

The BS was positive in 248 patients, and associated with a subsequent change of management in only 31%. Of the latter patients, 84.4% (65/77) were referred for PFO closure (Figure 1). The majority of changes to medications as a result of PFO detection occurred in those undergoing closure (70% or 28/40 patients). Expectedly, those commenced on antiplatelet therapy were more likely to undergo PFO closure than those who had a new anticoagulant commenced (17 vs 9, p = 0.013).

When assessing which patient characteristics affected management, younger patients (<45 years old) were more likely to undergo closure than those >65 years (OR 4.6 [95% CI 1.7–12.4], p = 0.003). Other predictors of closure included multi-territory stroke (OR 2.5 [95% CI 1.3–5.0], p = 0.007), being a non-smoker (OR 2.9 [95% CI 1.2–6.8], p = 0.016)

and the presence of aortic plaque (OR 3.6 [95% CI 1.8–7.5], p = 0.001). Patients who underwent PFO closure had a higher mean "modified" RoPE score than those who did not undergo a procedure (6.5 $\pm$ 1.9 vs 5.5 $\pm$ 1.9, p < 0.001). A sensitivity analysis (with multi-territory infarct being excluded from the "modified" RoPE score) demonstrated a similar trend (5.97 vs 5.25, p = 0.01). Public vs private insurance status did not influence the decision to close (54/197 vs 11/51 patients or 27.4% vs 21.6%, p = 0.48).

Of 924 bubble studies performed, one patient (0.1%) developed blurred vision and vertigo immediately following the contrast injection. This patient had undergone percutaneous closure and had a residual shunt. Repeat cerebral imaging was not performed. The symptoms resolved within 24 hours and a diagnosis of transient ischaemic attack was made. One patient developed aspiration pneumonia as a result of a transoesophageal echocardiogram (0.3%).

Discussion

In this large, multi-centre retrospective observational study, our local experience suggests that the echocardiographic "bubble study" is frequently performed in patients who have a readily identifiable cause of stroke. Whilst the "burden" of all transthoracic studies performed is 7.6%, we have demonstrated that PFO screening is commonly undertaken in patients who have multiple vascular risk factors and not infrequently in those with large vessel atherosclerosis, and even atrial fibrillation. The first implication of this over-screening is an increased burden on
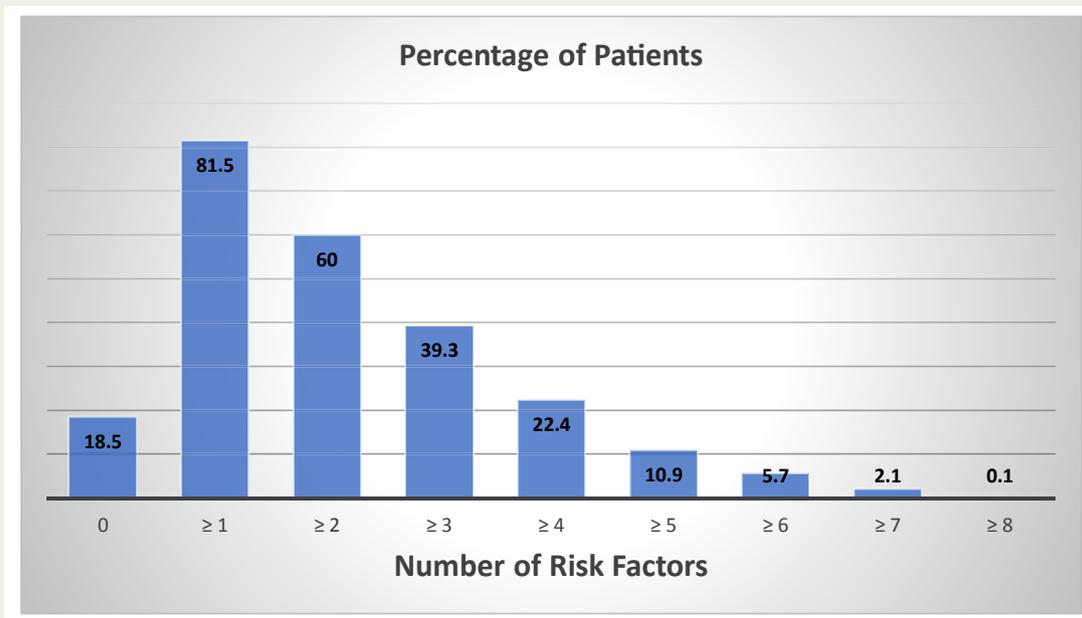
Figure 2 Assessment of cumulative risk factors in stroke patients undergoing a bubble study.

resources. Sonographers often have to ask for medical assistance for insertion of an intravenous cannula and to perform the BS itself, which adds delay to scanning times.

Longstanding and more recent definitions of cryptogenic stroke are based on what is *not present* in a standard workup (large vessel atherosclerosis, small vessel disease etc.) [21,24,25]. This concept served as an exclusion criterion in all of the PFO closure trials. After all, there would be little to gain from closing a PFO that did not relate to the stroke. In this study, 39.3% of patients who underwent screening with a BS had ≥3 conventional stroke risk factors. In such patients, it

is less likely that the PFO caused the stroke. Only 47.1% of patients had a ''modified'' RoPE score of >5. This is significant, as a RoPE score < 5 equates to < 50% chance that the PFO related to the stroke [9]. Furthermore, 34.7% of patients screened for PFO were >60 years old. In this age group, the likelihood of a non-PFO cause of ischaemic stroke increases (commonly subclinical atrial fibrillation) and thus caution would be needed in considering such patients for closure.

It has been highlighted that the recently published CLOSE and REDUCE papers have both focussed on what *is present* during a stroke work-up, in particular an aneurysmal septum
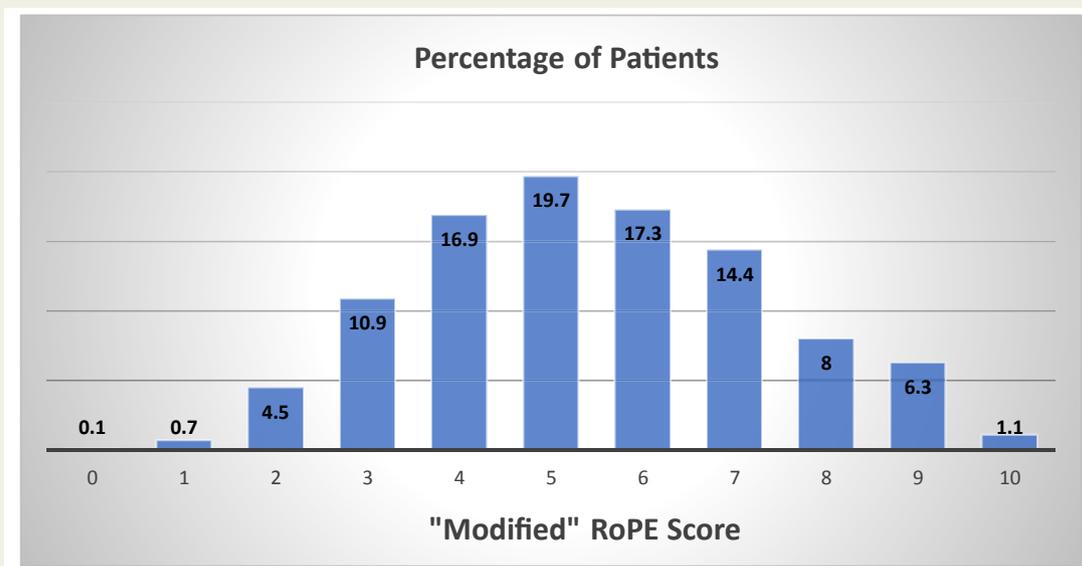

Figure 3 Assessment of ''Modified'' Risk of Paradoxical Embolism (RoPE) scores of stroke/TIA (transischaemic attack) patients undergoing a ''bubble study''.

and a moderate to large shunt [18,19,24]. Such criteria were not present for the long-term follow-up of the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial however, which also reported superiority of closure over medical therapy [17]. Regardless, it is clear that appropriate patient selection is key for improving outcomes from PFO closure. The authors of CLOSE noted that part of their success was enrolling patients with fewer vascular risk factors than previous trials [18].

Based on the results of this study, we would advocate for the use of the RoPE score early in the workup of a cryptogenic stroke. Patent foramen ovale screening using a BS should be directed at younger patients (aged <60 years) who lack significant vascular risk factors and who have high-risk echocardiographic features. Deferring a BS until prolonged cardiac monitoring has been undertaken would increase the detection of subclinical atrial fibrillation and prevent inappropriate PFO screening. By adopting these methods of practice, it will better discriminate the appropriate referrals for PFO closure and hopefully yield better outcomes.

The majority of patients found to have a PFO in this study had no subsequent change in their management. This may simply reflect that the PFO was not thought to be relevant to the stroke/TIA. The rate of referral for PFO closure was fairly rigorous however, at almost 30%. Furthermore, the majority of changes to either antiplatelet/anticoagulant therapy following PFO detection, occurred in preparation for a closure device. Expectedly, significant predictors of closure included younger age when >65 years was used as a reference (OR 4.6 [95% CI 1.7–12.4], p = 0.003) and multi-territory stroke (OR 2.5 [95% CI 1.3–5.0], p = 0.007). The ''modified'' RoPE score was higher in those who underwent closure (6.5 ± 1.9 vs 5.5 ± 1.9, p < 0.001). It is somewhat contradictory that aortic plaque detection was associated with a greater chance of PFO closure (OR 3.6 [95% CI 1.8–7.5], p = 0.001). However, this reflects that these patients underwent a TOE study, and so had a greater chance of plaque being noted.

The final implication of over-screening for PFO is unnecessary patient risk of procedural complication. The incidence of stroke or TIA (via an air embolism) as a complication of a BS is unknown. Previous studies have reported no adverse effects [26] to relatively frequent events [12,27]. Romero et al. reported five cases of cerebrovascular events following a BS. This was not a direct observational study however, but instead relied on physician members of an online forum responding to a questionnaire. They estimated that five adverse events occurred from 3314 ''bubble studies'' performed [12]. Ours is the largest observational study to date to assess the incidence of stroke or TIA from a BS. Of 924 patients assessed, one patient (0.1%) suffered a TIA as a procedural complication. Consistent with previous studies, we have demonstrated that the complication rate is low, but not so low that informed consent should not be obtained prior to a BS being performed.

We found PFO prevalence to be high (48%) in stroke patients without conventional risk factors. Whilst this does not prove cause and effect, it is consistent with previous data [28–34]. Interestingly however, whilst our aim was to demonstrate that PFO screening frequently occurs in inappropriately selected patients, the prevalence of PFO in the total stroke cohort was 34.7%, which is consistent with that seen in cryptogenic stroke patients and higher than the almost 25% prevalence seen in the general population [35].

In summary, whilst a transthoracic echocardiogram is an important investigation in cryptogenic stroke, there needs to be a strong focus on who should be investigated for PFO. Younger patients (i.e. <60 years) with an embolic (i.e. non-lacunar) ischaemic stroke who have high-risk echocardiographic features and who lack conventional stroke risk factors and other causes of embolic ischaemic stroke, may be more likely to benefit from further investigation. A more stringent approach will better discriminate appropriate patients for PFO closure referral, reduce resource burden and the exposure of patients to unnecessary risk, albeit small.

Study Limitations

Whilst we believe this study provides a useful insight into common clinical practices during the work-up of ischaemic stroke, it ultimately reflects practice at a local level and may not be generalisable. We used ''multi-territory'' stroke as a surrogate for ''cortical stroke'' when calculating the RoPE score, which may affect the accuracy of our data. Finally, our reported complication rate from a BS may be an underestimate given that this is a retrospective study and thus is subject to recall/reporting bias.

Disclosures

None. All authors contributed equally to this manuscript and have approved it for submission.

Funding

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2018.07.007.

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