Cardiac magnetic resonance imaging: a new tool to identify cardioaortic sources in ischaemic stroke

Shadi Yaghi,1 Ava L Liberman,2 Michael Atalay,3 Christopher Song,4 Karen L Furie,1 Hooman Kamel,5 Richard A Bernstein6

ABSTRACT
Stroke of undetermined aetiology or ‘cryptogenic’ stroke accounts for 30–40% of ischaemic strokes despite extensive diagnostic evaluation. The role and yield of cardiac imaging is controversial. Cardiac MRI (CMR) has been used for cardiac disorders, but its use in cryptogenic stroke is not well established. We reviewed the literature (randomised trials, exploratory comparative studies and case series) on the use of CMR in the diagnostic evaluation of patients with ischaemic stroke. The literature on the use of CMR in the diagnostic evaluation of ischaemic stroke is sparse. However, studies have demonstrated a potential role for CMR in the diagnostic evaluation of patients with cryptogenic stroke to identify potential aetiologies such as cardiac thrombi, cardiac tumours, aortic arch disease and other rare cardiac anomalies. CMR can also provide data on certain functional and structural parameters of the left atrium and the left atrial appendage which have been shown to be associated with ischaemic stroke risk. CMR is a non-invasive modality that can help identify potential mechanisms in cryptogenic stroke and patients who may be targeted for enrolment into clinical trials comparing anticoagulation to antiplatelet therapy in secondary stroke prevention. Prospective studies are needed to compare the value of CMR as compared to transthoracic and transesophageal echocardiography in the diagnostic evaluation of cryptogenic stroke.

BACKGROUND
Ischaemic stroke affects nearly 690 000 people in the USA every year, of which ~200 000 (30–40%) are considered of unknown cause or ‘cryptogenic’.1 2 Given the strong circumstantial evidence favouring an embolic aetiology of most cryptogenic strokes,3–4 investigators have recently used the term embolic stroke of undetermined source (ESUS) to describe non-lacunar stroke without evidence of ipsilateral extracranial or intracranial large artery stenosis of 50% or more, a major cardioembolic source such as atrial fibrillation (AF) or other specific mechanism of stroke.3 Identifying the root cause of ischaemic stroke is more than an academic issue, since the specific stroke subtype often guides secondary stroke prevention measures. For instance, detection of AF on outpatient cardiac monitoring usually leads to anticoagulant rather than antiplatelet therapy.6 The role and yield of cardiac imaging in the diagnostic evaluation of patients with ischaemic stroke is controversial. Cardiac MRI (CMR) has been used for cardiac disorders, but its utility in cryptogenic stroke is not well established. The aim of this paper is to explore the role of CMR in the diagnostic evaluation of patients with ischaemic stroke.

METHODS
We performed a narrative review of the literature on the use of CMR in the diagnostic evaluation of ischaemic stroke between 1 January 2010 and 30 June 2016. This literature included randomised trials, comparative studies and case series. We also searched the literature for comparative studies regarding the use of CMR as compared to transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE). These findings were interpreted in light of the yield of TTE and TEE in the diagnostic evaluation of ischaemic stroke from prior studies.

POTENTIAL MECHANISMS IN CRYPTOGENIC STROKE
There are several potential embolic sources that might result in stroke and yet be difficult to diagnose. These include paradoxical (venous to arterial) embolism via a patent foramen ovale (PFO), atheroma of the aortic arch, artery-to-artery embolism from atherosclerotic plaque that has not resulted in significant stenosis of the arterial lumen and paroxysmal cardiac arrhythmias such as AF.7

Unless AF is detected, antiplatelet therapy is considered to be the treatment of choice in most patients with cryptogenic stroke and evidence of a PFO thick aortic plaque (>4 mm)6 or non-stenosing complex intracranial or extracranial atherosclerosis.6

Paroxysmal AF is detected in up to 20–30% of patients with cryptogenic stroke on outpatient telemetry or implantable cardiac monitors6 and may be causative in many of these cases. When AF is captured on long-term monitoring, this frequently leads to anticoagulation therapy5–9 which is superior to antiplatelet therapy in secondary stroke prevention in patients with AF detected with standard measures.

Recently, ‘atrial cardioopathy’, as indicated by biomarkers of atrial dysfunction on ECG,10 11 echocardiographic12 and serum laboratory testing,13 has been suggested as a possible embolic source in cryptogenic stroke.14 In one study, atrial cardioopathy was present in up to 65% of patients with cryptogenic stroke.15 Patients with atrial cardioopathy might benefit from anticoagulation therapy for secondary stroke prevention, similar to patients with AF. One of the most promising indicators of

1Department of Neurology, The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA
2Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA
3Department of Radiology, The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA
4Division of Cardiology, Department of Internal Medicine, The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA
5Department of Neurology and Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, New York, New York, USA
6Department of Neurology, Feinberg School of Medicine of Northwestern University, Chicago, Illinois, USA

Correspondence to
Dr Shadi Yaghi, Department of Neurology, The Warren Alpert Medical School of Brown University, 353 Eddy Street APC 530, Providence, RI 02903, USA; shadiyaghi@yahoo.com

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atrial dysfunction and stroke risk is elevated serum NT-proBNP level. In contrast to the results in unselected patients in the WARSS trial, a post hoc analysis of the WARSS trial showed that warfarin was significantly better than aspirin at preventing recurrent stroke in those with NT-proBNP ≥750 ng/dL (HR 0.30, 95% CI 0.12 to 0.84; p=0.021).

CARDIAC IMAGING OF PATIENTS WITH ISCHEMIC STROKE
Of the common potential sources of cryptogenic stroke outlined above, many are integrally related to the cardiac system. Therefore, ideal strategies for cardiac imaging after a cryptogenic stroke are areas of active inquiry.

Echocardiography
Several studies showed that TTE and perhaps TEE are useful in identifying a potential cardiac source in patients with cryptogenic stroke. In one study, TEE was shown to be superior to TTE in identifying a potential cardiac source in 40% of patients with cryptogenic stroke who underwent TTE and TEE. The advantage of a TEE is that it provides better views of the left atrium (LA), left atrial appendage (LAA) and aortic arch. In addition, it is superior to TTE in identifying cardiac shunts such as PFO. TTE, however, is more widely used, non-invasive and less expensive when compared to TEE. Despite its superior diagnostic yield, TEE is infrequently performed after cryptogenic stroke due to the potential risks of a TEE and since many of the findings best identified on TEE do not have proven treatment implications.

Cardiac MRI
Echocardiography and some period of heart-rhythm monitoring currently comprise the standard cardiac evaluation of cryptogenic stroke. However, recent evidence raises the possibility that CMR may identify a specific cause in some proportion of cryptogenic strokes.

BACKGROUND ON CMR
Recently, CMR has rapidly emerged as an important non-invasive imaging modality in cardiovascular medicine. Its excellent spatial resolution and contrast, three-dimensional imaging capacity and ability to depict soft tissues have led to numerous applications in clinical cardiology. In fact, it has become the test of choice for several cardiovascular problems. For example, CMR is now considered the gold standard for non-invasive assessment of ventricular volume, mass and ejection fraction for left and right ventricles. Contrast-enhanced CMR allows for the evaluation of myocardial viability, fibrosis, scar, acute myocyte rupture and—more broadly—myocardial damage associated with any disease state that expands the extracellular volume (where contrast accumulates). CMR also has diagnostic and prognostic utility in the assessment of a wide range of cardiomyopathies (CM) such as hypertrophic CM, cardiac amyloidosis (figure 1), cardiac sarcoidosis (figure 1), non-ischaemic dilated CM and cardiac involvement in hemochromatosis, among many others. Vasodilator stress perfusion CMR can accurately identify patients with significant coronary artery disease and is superior to conventional nuclear methods in patients who are unable to exercise.

Other applications of CMR include evaluation of pericardial diseases, valvular heart disease and pulmonary vein imaging prior to radiofrequency ablation of AF. Moreover, CMR is equipped to fully characterise congenital heart lesions. In addition to its numerous strengths described above, CMR can delineate vascular anatomy with great precision through the use of angiographic techniques (magnetic resonance angiography, MRA) and, importantly, can quantify instantaneous blood velocity (in cm/s) and total blood flow (in cc/s) in large vessels using so-called phase contrast imaging. As well as permitting the characterisation of valve lesions, this latter method permits non-invasive quantification of shunt fraction (Qp/Qs) as a measure of the severity of an intracardiac or extracardiac shunt. This is a distinct advantage that CMR offers over TEE for the assessment of atrial septal defects (ASDs), for example.

Finally, CMR is the preferred imaging modality for characterising virtually all of the clinically pertinent features of cardiac masses, such as size, location, mobility and functional significance, and vascularity. The presence or absence of enhancement following contrast injection is particularly useful for clarifying whether intracavitary masses are thrombus (figure 2) or tumour (figure 3). This distinction is paramount for determining the appropriate clinical management (ie, surgical vs medical). In terms of the assessment of cardioembolic disease, CMR has been shown to have higher sensitivity and specificity for the detection of left ventricular thrombus when compared to TTE and TEE. Additionally, CMR and MRA excel in assessment of the aortic pathology such as atheroma, acute aortic injuries, including dissection and intramural haematomata, and aortitis.

CMR IN PATIENTS WITH CRYPTOGENIC STROKE
There is increasing recognition that CMR may provide significant advantages in identifying embolic sources in patients with unknown ischaemic stroke mechanisms. Single-centre studies of patients who had ischemic stroke suggest that CMR should be considered in the diagnostic evaluation of some patients. The largest study to date found that the addition of CMR to standard diagnostic evaluation among 85 consecutive patients resulted in a significant reduction in the number of patients who had stroke classified as cryptogenic stroke (from 27% to 20%). Of the 23 patients who had cryptogenic stroke initially identified following a standard diagnostic evaluation which included TTE (but not TEE), six patients had well-established sources of potential embolism identified by CMR and three additional patients were found to have ≥3 segments of transmural ventricular scarring on delayed enhancement (DE)-CMR suggestive of embolic source. Of the six patients with cardiac sources identified only on CMR, three had an evident embolic source (left ventricular thrombus in two patients and a complex ascending aortic thrombus in one patient). In the remaining three patients, CMR detected a possible embolic source (intra-atrial septal aneurysm in two patients and PFO and intra-atrial septal aneurysm in one patient). Another study included 101 patients with ischaemic stroke or TIA and compared cardiac CT (CCT) to echocardiography using CMR when needed as the reference standard. This study demonstrated that CCT following ischaemic stroke found evidence of large myocardial infarction in nine patients (6%) who had only normal or mild hypokinesia noted on echocardiography; CMR studies confirmed these CCT findings. Rates of cryptogenic stroke reclassification were not reported in this second study.

The added benefit of CMR in unselected patients with cryptogenic stroke who have completed a diagnostic evaluation including TTE and TEE remains unclear. Although TEE would not be expected to be more sensitive for ventricular scarring than TTE, a small prospective pilot found that CMR was actually less sensitive than TEE for detecting possible embolic sources among patients who had non-lacunar stroke.
However, another study found that aortic plaques in patients who had ischemic stroke were more frequently detected by three-dimensional (3D) 3T MRI of the aorta than TEE. Among participants with cryptogenic stroke (n=26), aortic MRI identified high-risk embolic sources that were not seen on TEE in 8 participants (30.8%). Notwithstanding these small studies, whether CMR provides useful information beyond TEE in patients who had cryptogenic stroke requires further investigation.

Some atypical, congenital and underappreciated structural cardiac abnormalities have been identified using CMR in patients who had cryptogenic stroke. A systematic study of CMR in identifying these less common entities is lacking. Case reports of CMR have reported left ventricular non-compaction, an uncommon congenital cardiomyopathy associated with cardioembolic risk, after cryptogenic stroke. There are also reports of Raghib syndrome, a rare developmental anomaly marked by persistence of the left superior vena cava along with coronary sinus ostial atresia and ASD; as well as endomyocardial fibrosis. None of the studies, however, designed to evaluate the role of CMR in acute stroke diagnostic evaluation report on left atrial or LAA features among included patients despite recent work on atrial cardiopathy as a potential stroke mechanism in patients who had cryptogenic stroke.

CMR IN THE EVALUATION OF THE LA
Left atrial enlargement
The clinical implications of enlargement of the LA are manifold. In population-based studies, LA enlargement (LAe) is associated with increased overall stroke risk and cardiovascular mortality. The presence of AF has long been associated with the finding of LAe, though the temporal relationship between these two entities is not well understood. Recent work, however,
Figure 3  Transaxial (A) precontrast and (B) postcontrast MR images demonstrate an enhancing LA mass (arrows). This appearance combined with other imaging findings (not shown) excludes thrombus and is virtually diagnostic of myxoma which was confirmed at surgery. LA, left atrial; RA, right atrium.

has found that moderate-to-severe LAE is associated with a higher risk of recurrent cryptogenic or cardioembolic stroke, even after adjusting for AF.12

Using CMR to further clarify association between LAE and embolism is an intriguing area of future research. CMR is considered the gold standard for the evaluation of LAE as it allows for 3D reconstruction of the LA acquired with high spatial and temporal resolution.41 Echocardiographic measurements of the LA are often challenging due to the oblique position of the interatrial septum and the long and narrow LA appendage.42 There are a number of different methods to calculate left atrial volume using images from TTE, but every method depends on operator-dependent measurements using geometric assumptions to determine volume. Two-dimensional (2D) TTE and 3D TTE systematically underestimate LA volume compared to CMR by up to 37%.43 When the measured volume of eight cadaveric atrial casts was compared between MRI and the water displacement method, the correlation between the two modalities was excellent further suggesting MRI is particularly accurate for estimations of atrial volume.44

LA fibrosis
An accumulation of fibrillar collagen deposits in the myocardium of the LA, LA fibrosis, is a common feature of clinical AF.45 Atrial fibrosis is likely less well studied than LAE because the former is difficult to evaluate. Invasive electrophysiological techniques can be used to characterise atrial fibrosis, but most non-invasive imaging modalities such as echocardiography are not particularly useful in detecting fibrosis as the thin walls of the atria necessitate significant image resolution.46 47 DE-CMR has gained prominence in providing a useful non-invasive means to characterise and quantify fibrosis. Among patients with AF, DE-CMR has been used to detect fibrosis prior to ablation48 as well as to identify scarring of the atrium following radiofrequency ablation.49 More recent work has shown that DE-CMR can also be used to detect LA fibrosis in a general cardiology population, including among those without structural heart disease or AF.50

Detection of LA fibrosis may be helpful in estimating the risk of clinically relevant outcomes including stroke. In a large prospective multicentre observational cohort study, the presence of atrial tissue fibrosis on DE-CMR was independently associated with the likelihood of recurrent AF following catheter ablation of AF (HR per 1% increase in fibrosis of 1.06).51 Furthermore, a multicentre retrospective study using DE-CMR demonstrated an association between LA fibrosis and history of stroke. Among patients with AF who underwent DE-MRI before pulmonary vein isolation, the 36 (9.3%) who had a documented prior stroke had a significantly higher percentage of LA fibrosis (24.4 ±12.4% vs 16.1±9.8%). A regression analyses controlling for known stroke predictors found that LA structural remodelling quantified by DE-MRI was independently associated with stroke.52 This study, however, is limited by the small number of patients with prior stroke and the fact that all patients had a history of AF.53 Whether DE-CMR is associated with ischaemic stroke in the absence of AF remains unclear. However, proving this association may lead to clinical trials studying anticoagulation versus antiplatelet therapy for secondary stroke prevention strategy in this patient population.

CMR IN THE EVALUATION OF THE LAA
The LAA is the remnant of the embryonic LA, a largely non-functional structure. The LAA has long been considered to be a prime site for thrombus formation in patients with AF. In a pooled analysis of 23 studies (4792 patients with AF undergoing TEE, cardiac surgery or autopsy), left atrial thrombi were detected in ~14% of patients, and the majority of which were in the LAA.54 Therefore, a better understanding of the anatomy and physiology of the LAA using various imaging modalities may be of value in advancing our understanding of stroke aetiology. The LAA varies significantly in shape, size and orientation relative to adjacent cardiac structures.55 A study of 500 postmortem hearts demonstrated that the LAA most commonly has two lobes (54%), followed by three lobes in 23%, one lobe in 20% and four lobes in 3%.56 The number of lobes has been shown to be an independent risk factor for the presence of thrombus.57 Furthermore, studies have shown an association between ischaemic stroke and specific LAA morphologies in patients with AF. A retrospective study of 932 patients with AF categorised the LAA into four distinct morphologies: chicken wing (48%), cactus (30%), windsock (19%) and cauliflower (3%) (figure 4) and found that non-chicken wing LAA morphology was associated most strongly with ischaemic stroke.58 Another case–control study, however, showed that each of chicken wing and cauliflower morphologies are more common in patients who had ischaemic stroke when compared to controls.59 These findings allude to a direct mechanistic relationship between LAA morphology and embolic risk.
CMR has recently been used to characterise the LAA morphology, determine the number of LAA lobes and detect LAA thrombi and fibrosis. DE-CMR may also be used to detect LAA structure-related dysfunction. Recent evidence showed that LAA fibrosis on CMR is associated with reduced LAA peak flow velocities as measured by echocardiography, suggesting that fibrotic changes of the LAA appendage are linked to stasis, thrombus formation and stroke risk. When compared to other imaging modalities, such as TEE, CMR is at least as good as TEE in determining the number of LAA lobes and detecting thrombi. Furthermore, CMR may be superior to TEE in characterising LAA morphology and detecting fibrotic changes, which may constitute a potential stroke mechanism in this patient population. Flow velocity in the LAA orifice as measured by TEE has been shown to predict ischaemic stroke risk in patients with AF. With phase contrast imaging, CMR may also permit measuring the LAA flow velocity, but this method is still not well established in the literature.

Therefore, CMR may be a useful tool in the diagnostic evaluation of patients with cryptogenic stroke allowing better understanding of the LAA structure and function, which in turn helps understand the recurrent stroke risk, leading to trials designed to improve secondary stroke prevention strategies after a cryptogenic stroke.

COST-EFFECTIVENESS

In addition to questions about its tolerability and utility in the evaluation of stroke, the role of CMR will need to be guided by its cost-effectiveness. Although CMR is not an inexpensive test, it may be cost-effective if it (1) replaces another test, such as TEE; (2) is more quickly obtainable in inpatient settings than equivalent tests and thus leads to shorter lengths of stay and/or (3) it increases the detection of underlying pathologies whose recognition triggers evidence-based changes in treatment that in turn result in better clinical outcomes. For example, detection of cardiac thrombus may lead to a change from antiplatelet to anticoagulant therapy; although such a treatment change is not based on direct evidence from randomised clinical trials, the WARCEF trial did show a significant reduction in ischaemic stroke with warfarin as compared to aspirin in patients with heart failure. This benefit, however, was outweighed by the risk of intracerebral haemorrhage with warfarin, and the primary composite end point of ischaemic stroke, haemorrhagic stroke or death was similar between the two groups. Alternatively, CMR may lead to detection of subclinical coronary artery disease that may trigger beneficial changes in medical treatments and closer follow-up with cardiologists. If further research indicates that one or more of the above factors pertain to CMR, then this diagnostic test may prove cost-effective, as seen in studies of its use in the diagnosis of coronary disease and as seen in other diagnostic tests used for stroke evaluation.

CONCLUSIONS

There is a potential role for CMR in the diagnostic evaluation of patients with cryptogenic stroke to identify potential aetiologies such as cardiac thrombi, cardiac tumours, aortic arch disease and other rare cardiac anomalies. It can also provide data on certain functional and structural parameters of the LA and the LAA associated with ischaemic stroke risk. In the future, these CMR biomarkers may help guide the design of clinical trials investigating anticoagulation versus antiplatelet therapy for secondary prevention of cryptogenic stroke.

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Figure 4 Shaded-surface reconstructions of MRA data sets obtained from four different patients demonstrate various LAA morphologies (arrows), including (A) ‘chicken-wing’, (B) ‘cactus’, (C) ‘windsock’ and (D) ‘cauliflower.’ Dotted lines roughly correspond to the os of each LAA. The left superior (*) and inferior (arrowheads) pulmonary veins are indicated. LAA, left atrial appendage; MRA, magnetic resonance angiography.
Cerebrovascular disease

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