Original Contribution

Feasibility and Diagnostic Value of Cardiovascular Magnetic Resonance Imaging After Acute Ischemic Stroke of Undetermined Origin

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Background and Purpose—Etiology of acute ischemic stroke remains undetermined (cryptogenic) in about 25% of patients after state-of-the-art diagnostic work-up.

Methods—One-hundred and three patients with magnetic resonance imaging (MRI)–proven acute ischemic stroke of undetermined origin were prospectively enrolled and underwent 3-T cardiac MRI and magnetic resonance angiography of the aortic arch in addition to state-of-the-art diagnostic work-up, including transesophageal echocardiography (TEE). We analyzed the feasibility, diagnostic accuracy, and added value of cardiovascular MRI (cvMRI) compared with TEE for detecting sources of stroke.

Results—Overall, 102 (99.0%) ischemic stroke patients (median 63 years [interquartile range, 53–72], 24% female, median NIHSS (National Institutes of Health Stroke Scale) score on admission 2 [interquartile range, 1–4]) underwent cvMRI and TEE in hospital; 89 (86.4%) patients completed the cvMRI examination. In 93 cryptogenic stroke patients, a high-risk embolic source was found in 9 (8.7%) patients by cvMRI and in 11 (11.8%) patients by echocardiography, respectively. cvMRI and echocardiography findings were consistent in 80 (86.0%) patients, resulting in a degree of agreement of $\kappa=0.24$. In 82 patients with cryptogenic stroke according to routine work-up, including TEE, cvMRI identified stroke etiology in additional 5 (6.1%) patients. Late gadolinium enhancement consistent with previous myocardial infarction was found in 13 (14.6%) out of 89 stroke patients completing cvMRI. Only 2 of these 13 patients had known coronary artery disease.

Conclusions—Our study demonstrated that cvMRI was feasible in the vast majority of included patients with acute ischemic stroke. The diagnostic information of cvMRI seems to be complementary to TEE but is not replacing echocardiography after acute ischemic stroke.

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Etiologic work-up is essential in patients with acute ischemic stroke to optimize secondary stroke prevention. According to international guidelines, state-of-the-art diagnostic work-up includes brain imaging, ultrasound of brain-supplying arteries, echocardiography, ECG monitoring, and distinct blood tests.[1,2] However, stroke etiology remains undetermined (cryptogenic) in about 25% of all acute ischemic stroke patients.[3] Apart from nonpermanent atrial fibrillation (AF),[4] ventricular noncompaction, left atrial or ventricular thrombi, mitral or aortic valve stenosis, and ulcerated aortic arch atherosclerotic plaques are associated with a moderate to high embolic stroke risk and were found in a substantial part

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of cryptogenic stroke patients undergoing echocardiography.[5] Despite interstudy variations on the definition and prevalence of (potential) embolic sources, current guidelines recommend diagnostic echocardiography in stroke patients.[2]

Although noninvasive transthoracic echocardiography (TTE) is easy to use, semi-invasive transesophageal echocardiography (TEE) is typically needed to visualize the left atrium, left atrial appendage, atrial shunts, and the aortic arch—all of them potential sources of embolism.[6] Serious complications during TEE rarely occur.[7] However, required preprocedural fasting, periprocedural conscious sedation, and the demand of highly skilled personnel limit its availability and cause in-hospital delays.[8] In consequence, TEE is not routinely performed in (cryptogenic) stroke patients, even in high-income countries.[9] Subsequently, assessment of potential embolic sources of ischemic stroke is often inappropriate in clinical practice. Although cardiac computed tomography could add information about stroke etiology,[10] the main disadvantage of this approach is the exposure to radiation. Cardiac magnetic resonance imaging (MRI) has been increasingly often implemented in the clinical diagnostic workflow of various cardiac diseases over the past 10 years and allows for accurate biventricular functional analysis and tissue characterization. Cardiac MRI is now considered the gold standard to assess cardiac tumors, myocarditis, cardiomyopathies, and subclinical coronary heart disease.[11,12] In addition, cardiac MRI has demonstrated feasibility of detecting atrial or ventricular thrombi,[13] aortic atherosclerotic plaques,[14,15] or left atrial enlargement.[16,17] Moreover, cardiac MRI is superior to echocardiography on detection of recent or previous myocardial infarction.[18,19] Although a few MRI studies reported the prevalence of specific (potential) embolic sources after stroke,[15,20–22] these studies did not provide a comprehensive statement on the diagnostic value of cardiovascular MRI (cvMRI) compared with the current gold standard of TEE and TTE assessment of acute ischemic stroke etiology.

Therefore, we assessed the feasibility and safety of noninvasive cvMRI in patients with acute ischemic stroke. The main aim of the prospective CaMRISS (Cardiac MRI for the Assessment of Cardioembolic Sources in Ischemic Stroke Study) was to assess the clinical impact of cvMRI compared with TEE/TTE to detect potential cardiac and aortic embolic sources of acute ischemic stroke.

Methods

Study Design and Study Population

The investigator-initiated, prospective, single-center CaMRISS study was sponsored and conducted by the Center for Stroke Research Berlin at the Campus Benjamin Franklin, Charité - Universitätsmedizin Berlin, Germany. The Charité Ethics Committee approved the study protocol (EA4/073/10). The primary hypothesis was that the diagnostic value of contrast medium-enhanced cvMRI and TEE coincides with regard to detection of cardioaortic embolic sources in patients with acute ischemic stroke. The secondary hypothesis was that contrast medium-enhanced cvMRI detects a potential embolic source of embolism in about 20% of all patients with so far cryptogenic stroke. Stroke patients who fulfilled the inclusion and exclusion criteria (Table 1) and gave written informed consent were enrolled from January 2011 to November 2013 (details can be found in the online-only Data Supplement). In addition to cvMRI and brain MRI, study patients underwent TEE, carotid and transcranial duplex ultrasonography of brain-supplying arteries, stroke unit/ECG monitoring for ≥24 hours, and blood sampling. Echocardiography was performed in accordance with the Guidelines of the European Society of Cardiology.[23] The majority of study patients (n=79) underwent TTE in addition to TEE. Experienced cardiologists performing echocardiography (S.J., A.J.M.) were blinded to cvMRI findings. Blinded brain MRI and magnetic resonance angiography reading was done by a board certified radiologist (J.B.F.). Cardiac MRI scans were analyzed by a cardiologist experienced in cardiovascular imaging (H.-C.E.,C.C.D.) and supervised by one of the board certified imaging experts (C.J., O.B.). Details on TEE/TTE, brain MRI and cvMRI can be found in the in the online-only Data Supplement. Stroke subtype classification according to the SSS-TOAST algorithm[24] was done by blinded investigators and based on in-hospital diagnostic evaluation (before and after enrollment). The presence of extended transmural myocardial scarring (indicated by late gadolinium enhancement [LGE]) and subsequent hypo- or akinesia in ≥3 wall segments was considered a relevant source of thrombus formation[13] and subsequent cardioembolism, as done by others.[25]

Table 1. Inclusion and Exclusion Criteria of the CaMRISS Study

Inclusion criteria	
	Written informed consent
	Age ≥18 y
	Acute ischemic stroke
	Enrollment within 48 h after stroke onset
	Cryptogenic stroke (according to SSS-TOAST criteria) on enrollment
	Scheduled for transesophageal echocardiography by the treating physician
Exclusion criteria	
	Contraindications for brain or cardiac MRI or known allergic reaction to Gadobutrol
	Contraindication to undergo transesophageal echocardiography
	Unable to cooperate with multiple breath-holds of a few seconds
	Glomerular filtration rate <30 mL min^{-1} 1.73 m^{-2} (Cockcroft–Gault formula)
	Pregnancy or lactation

CaMRISS indicates Cardiac MRI for the Assessment of Cardioembolic Sources in Ischemic Stroke Study; and MRI, magnetic resonance imaging.

Sample Size Calculation and Statistical Methods

To achieve a power of 80% at a significance level of P=0.05 in the 1-sided κ test H0: κ <0.80 versus HA: κ ≥0.80, if actual κ of the alternative is 0.95, we needed to calculate with at least 82 patients for the primary end point. Given a presumed dropout rate of 20%, 103 patients had to be included. Demographic data, cardiac findings, and feasibility outcomes were summarized with absolute and relative frequencies of qualitative characteristics and medians and interquartile ranges (IQRs) for quantitative variables. Statistical analyses were performed with SPSS (Version 23, SPSS Inc) and R. Frequencies are reported as n (%), and quantitative data are expressed as mean (SD) or median (quartiles), depending on the distribution of the data. Cohen κ was calculated to determine the interrater agreement for dichotomous and ICC for continuous data. The κ test for agreement between 2 raters was applied.[26] P values <0.05 were considered as statistically significant.

Results

Baseline Characteristics of Study Patients

The median age of the enrolled 103 stroke patients was 63 years (IQR, 53–72), 25 (24.3%) were female. The median NIHSS (National Institutes of Health Stroke Scale) score on admission was 2 (IQR, 1–4). The coexisting cardiovascular risk profile and rate of thrombolysis are summarized in Table 2.

Feasibility of cvMRI and Echocardiography in Acute Stroke Patients

Although 1 patient refused to undergo cvMRI after enrollment, 102 (99.0%) of 103 stroke patients underwent cvMRI during the initial in-hospital stay (median length 5 days [IQR, 4–6]). In total, 89 (86.4%) patients completed the cvMRI protocol (median duration 50 min [IQR, 42–58.5 min]) in hospital. In 4 patients, cvMRI was stopped as requested by the patient (because of claustrophobia, dyspnea, knee pain, or incompliance). In 5 patients, cvMRI was stopped because of poor image quality (because of motion artifacts or inability to cooperate with multiple breath-holds of a few seconds, respectively). These patients tolerated a median scanning time of 33 minutes (IQR, 19.5–43.5). In 3 patients, cvMRI examination had to be stopped because of the urgent need to do a brain MRI in another hyperacute stroke patient. Gadobutrol was not given to 1 patient because of renal insufficiency but was well tolerated by all other patients.

Overall, 102 (99.0%) of 103 study patients underwent TEE during the initial in-hospital stay, and 101 (98.1%) study patients completed the procedure. One patient refused to undergo TEE after being reinformed about the potential risks of the procedure, and another patient could not tolerate the probe. Additional TTE was done in 79 (76.7%) study patients. In 69 (67.6%) study patients, echocardiography was performed before cvMRI. The median delay between hospital admission and in-hospital cvMRI or echocardiography was 66.2 hours (IQR, 48.1–92.3) or 50.2 hours (IQR, 35.5–89), respectively.

Table 2. Baseline Characteristics of 103 Stroke Patients Enrolled to the CaMRISS Study

Age, y; median (IQR) [range]	63 (53–72) [31;83]
Female, % (n)	24.3 (25)
NIHSS score, median (IQR) [range]	2 (1–4) [0–16]
Application of intravenous r-tPA, % (n)	17.5 (18)
Cardiovascular risk profile, % (n)	
Hypertension	68.9 (71)
Diabetes mellitus	11.7 (12)
Chronic heart failure	1.0 (1)
Coronary artery disease	8.7 (9)
Previous stroke	27.2 (28)
Known malignancy	8.8 (8)
Hyperlipidemia	52.4 (54)

CaMRISS indicates Cardiac MRI for the Assessment of Cardioembolic Sources in Ischemic Stroke Study; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

Detection of Embolic Sources by cvMRI Versus Echocardiography

An embolic source of stroke was found in 11 (10.7%) study patients according to cvMRI and in 13 (12.6%) study patients according to echocardiography. A thrombus in the left ventricular apex was detected by TTE in 1 patient (who had previously been described having a ventricular thrombus according to echocardiography), whereas cine MRI did not demonstrate a thrombus. In this patient, cvMRI had to be terminated before application of contrast agent. Endocarditis was suspected in 2 (2.0%) of 102 patients according to TEE and in one of these patients according to cvMRI, respectively. In one of these patients, a TEE-detected endocarditis on mitral valve prosthesis was not imaged by cvMRI after stopping the MRI examination within minutes because of the patients' inability to hold the breath for a few seconds. Aortic arch atherosclerotic plaques (≥4 mm or ulcerated) were found in 6 (5.8%) of 102 patients according to TEE and in 3 of these patients according to contrast-enhanced cvMRI. cvMRI was stopped before starting the magnetic resonance angiogram in 2 stroke patients with complex atherosclerotic plaques according to TEE. One patient showed severely reduced left ventricular function (EF≤30%) according to TTE and cvMRI. Regional abnormalities of myocardial wall motion were present in 4 (3.9%) patients according to echocardiography and in 12 (11.8%) patients according to cvMRI. Takotsubo cardiomyopathy was detected in 1 patient by echocardiography and cvMRI (Figure). An atrial shunt (patent foramen ovale or atrial septum defect) was detected by echocardiography in 33 (32.2%) of 102 study patients and in 3 of these patients according to contrast-enhanced cvMRI (done in 31 of 33 patients). An atrial shunt was suspected by cvMRI in 2 patients without atrial shunt according to TEE.

A first episode of AF was detected after enrollment but during the in-hospital stay (median 5 days [IQR, 4–6], range 1–17 days) in 5 (4.9%) study patients. cvMRI or echocardiography revealed left atrial enlargement in 3 of these patients. In 1 AF patient, Takotsubo cardiomyopathy was suspected; another AF patient had cvMRI findings suspicious of subacute myocarditis.

Presence of Myocardial Infarction

Overall, 89 stroke patients completed the cvMRI. LGE indicating myocardial scarring was detected in 16 (18.0%) of these 89 patients (Table I in the online-only Data Supplement). Whereas 3 (3.4%) patients showed epicardial LGE, consistent with previous myocarditis, 13 (14.6%) patients demonstrated a subendocardial or transmural LGE, indicating previous myocardial infarction. Of these 13 patients, 7 (63.8%) patients with ischemic lesions had corresponding regional motion abnormalities according to cvMRI. In 4 patients, LGE was present in ≥3 dysfunctional left ventricular wall segments (range 3–7). Echocardiography missed 9 patients with MRI-detected previous myocardial infarction and demonstrated similar findings in 4 patients. Two of these 13 patients with LGE had a history of coronary artery disease (Table I in the online-only Data Supplement), and 1 patient was diagnosed to have a non–ST-segment–elevation myocardial infarction on admission. TTE and TEE were completed by 10 of 11 patients without known coronary artery disease but LGE

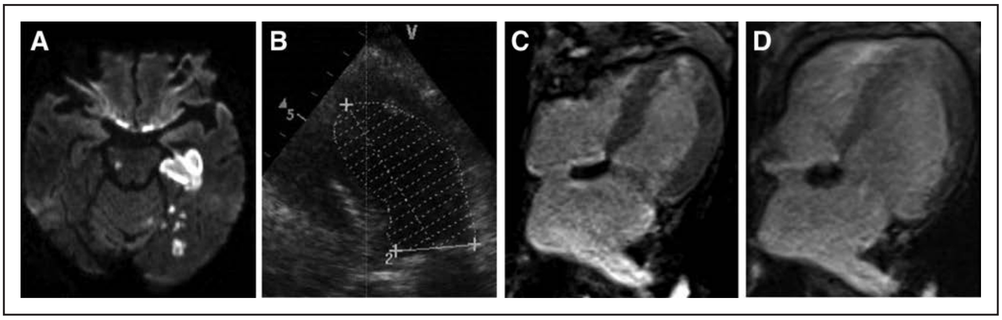

Figure. Takotsubo cardiomyopathy in an 83-year-old female patient with magnetic resonance imaging (MRI)–proven acute ischemic stroke (**A**, diffusion-weighted imaging) affecting the left middle cerebral artery and a first episode of atrial fibrillation in hospital. Takotsubo cardiomyopathy was detected by echocardiography (**B**, apical 4-chamber view, end systole) and cardiovascular MRI (cvMRI; **C**, long-axis cine images 4-chamber end-systolic image; **D**, 4-chamber end-diastolic image) demonstrating typical apical ballooning.

consistent with previous myocardial infarction. A corresponding regional wall motion abnormality was detected by echocardiography in one of these patients.

Stroke Etiology According to cvMRI Versus Echocardiography in Patients With Cryptogenic Stroke

At hospital discharge, stroke etiology was defined based on SSS-TOAST criteria as depicted in Table 3. Echocardiographic findings added substantial information for determining stroke etiology in 11 (11.8%) of 93 patients with otherwise cryptogenic stroke, whereas cvMRI findings were substantial in 9 (8.7%) patients. In 80 (86.0%) of these 93 stroke patients, cvMRI and echocardiographic findings were consistent. An embolic source of stroke was only detected by echocardiography in 7 (7.5%) patients and by cvMRI in 5 (5.4%) patients, respectively (Table 4). The degree of agreement for both imaging modalities was κ=0.24 and therefore significantly lower than the hypothesized value of κ=0.80 (P<0.001). Restricting the analysis to those 79 cryptogenic patients (according to standard diagnostic care in-hospital) completing cvMRI and TEE, the degree of agreement for both imaging modalities was κ=0.47.

Impact of cvMRI on Medical Stroke Prevention

In our department, acetylsalicylic acid and statins are standard in patients with acute ischemic stroke and without AF. Therefore, prescription of oral anticoagulation or dual antiplatelet therapy and an increased daily statin dose, if also taken before admission, indicated a change in standard medical stroke prevention. Overall, cvMRI findings led to a change in medical secondary stroke prevention in 6 stroke patients. One patient (without known coronary artery disease) received oral anticoagulation (because of AF) and additional acetylsalicylic acid one daily because cvMRI demonstrated LGE consistent with previous myocardial infarction. In addition, 4 of 11 patients with cvMRI-detected previous myocardial infarction received a higher statin dose before hospital discharge to achieve low-density lipoprotein cholesterol levels <70 mg/dL. Another stroke patient with MRI-detected (but TEE missed) aortic plaques was prescribed high-dose statin therapy for the first 3 months after stroke. Five of these 6 patients were classified as cryptogenic stroke according to standard diagnostic care, including echocardiography (Table 3).

Discussion

CaMRISS is the largest prospective study demonstrating feasibility of a comprehensive cvMRI protocol in patients with acute ischemic stroke. In addition, CaMRISS is the first study comparing the diagnostic value of 3-T cvMRI to echocardiography in patients who had otherwise undetermined etiology according to routine diagnostic work-up. Missing the predefined primary and secondary end point of the study focusing on determining stroke etiology, our findings indicate that the diagnostic information of cvMRI seems to be complementary to TEE but is not replacing echocardiography after acute ischemic stroke. A main finding of our prospective study was the relatively high rate of MRI-detected LGE, indicating clinically silent myocardial infarction in 12% of all stroke patients without known CAD.

Semi-invasive TEE in combination with noninvasive TTE is regarded as the present gold standard to detect (potential) cardiac and aortic sources of embolism in patients with acute ischemic stroke. However, feasibility of echocardiography—especially TEE—is limited in clinical practice even in high-income countries,[8,9] and TEE cannot be performed in some stroke patients for various reasons. Despite the fact that major cardioembolic risk sources can be detected by TEE/TTE and cvMRI,[2,13,15] available data on feasibility of cvMRI after acute ischemic stroke are limited to 1 observational study, including 83 unselected patients, not reporting feasibility in detail.[25] According to CaMRISS, 86% of selected stroke patients without existing MRI contraindications (Table 1) completed cvMRI, including application of contrast agent in hospital. Further technical improvements will shorten scanning time (≈50 min in CaMRISS), and a higher availability of cvMRI will probably increase the feasibility of cvMRI in the future.

The diagnostic value of cvMRI compared with TEE and TTE in (acute) ischemic stroke patients was unknown to date because previous studies—published during the conduct of CaMRISS—either used TEE in 20 (comparably) young patients within 90 days after nonlacunar ischemic stroke[27] or TTE only.[25] As also indicated by Baher et al,[25] the prevalence of high-risk embolic sources was comparably low after acute ischemic stroke (Table 4). Of note, high-risk embolic sources detected by echocardiography (like a ventricular thrombus or severe aortic plaques) were missed if cvMRI examination was terminated before the application of contrast agent.

Table 3. Stroke Cause at Hospital Discharge in 103 CaMRISS Patients

Etiology Index Stroke	Routine Diagnostic Work-Up			
	TEE/TTE, No; cvMRI, No	TEE/TTE, Yes; cvMRI, No	TEE/TTE, No; cvMRI, Yes	TEE/TTE, Yes; cvMRI, Yes
Cardioembolic	5 (4.9%)	11 (10.7%)	11 (10.7%)	15 (14.6%)
LAA	2 (1.9%)	7 (6.8%)	5 (4.9%)	8 (7.8%)
Small AD	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)
Other cause	2 (1.9%)	2 (1.9%)	2 (1.9%)	2 (1.9%)
Cryptogenic	93 (90.3%)	82 (79.6%)	84 (81.6%)	77 (74.8%)

Routine diagnostic work-up included brain MRI, ultrasound of brain-supplying arteries, laboratory results and ECG-monitoring in hospital for ≥24 h. TEE/TTE and cvMRI findings were taken into account (Yes) or not taken into account (No) for classification. AD indicates artery disease; CaMRISS, Cardiac MRI for the Assessment of Cardioembolic Sources in Ischemic Stroke Study; cv, cardiovascular; LAA, large artery atherosclerosis; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

The additional diagnostic value of cvMRI compared with echocardiography was demonstrated in CaMRISS patients who completed the examination. Although LGE was present in 18% of these patients, 14% had a subendocardial or transmural lesion, consistent with (previous) myocardial infarction (Table I in the online-only Data Supplement).[19] Of note, TEE and TTE revealed pathological findings in only 1 of 11 patients without known coronary artery disease and LGE consistent with previous myocardial infarction. Our finding is in line with Baher et al[25] who reported a noncoronary artery disease scarring in 15% of unselected stroke patients with a mean age of 66.3 years. In CaMRISS, 4 of these patients had a LGE of ≥3 dysfunctional wall segments (Table 4), indicating an independent risk factor for thrombus formation as shown in a previous study.[13]

In accordance with previous publications, including either 25[21] or 75 patients with cryptogenic stroke,[22] respectively, contrast-enhanced cvMRI failed to properly assess left atrial shunts in CaMRISS patients. Despite of the fact that a patent

Table 4. Pathological Findings of Echocardiography and cvMRI Impacting on Stroke Cause in All CaMRISS Patients

Sex	Age, y	Standard of Care	TEE/TTE Findings	cvMRI Findings	Stroke Cause
M	51	NRF	PFO+ASA (11 mm)	No atrial shunt	CE
M	55	NRF	NRF	LGE+WMA (4)*	CE
M	73	NRF	PFO+ASA (15 mm)	No atrial shunt	CE
M	70	NRF	NRF	LGE+WMA (7)*	CE
M	71	NRF	Aortic plaques ≥4 mm	Stopped before contrast	LAA
M	78	NRF	NRF	LGE+WMA (3)*	CE
M	75	NRF	Aortic plaques ≥4 mm	Stopped before contrast	LAA
F	78	NRF	Endocarditis	Endocarditis	CE
M	61	NRF	NRF	LGE+WMA (3)*	CE
M	64	NRF	NRF	Aortic plaques ≥4 mm	LAA
M	57	NRF	PFO+ASA (25 mm)	No atrial shunt	CE
M	72	NRF	Endocarditis	Stopped before contrast	CE
F	73	NRF	Aortic plaques ≥4 mm	Aortic plaques ≥4 mm	LAA
M	53	NRF	Ventricular thrombus+EF<30%	Stopped before contrast; EF<30%	CE
F	74	NRF	Aortic plaques ≥4 mm	Stopped before contrast	LAA
M	52	NRF	Aortic plaques ≥4 mm	Aortic plaques ≥4 mm	LAA
F	83	AF	Takotsubo cardiomyopathy	Takotsubo cardiomyopathy	CE
M	69	AF	PFO+ASA	Atrial shunt+LGE	CE

Standard of care included ultrasound of brain-supplying arteries, brain MRI, laboratory results, ECG monitoring ≥24 hours in hospital. AF indicates atrial fibrillation; ASA, atrial septum aneurysm; CaMRISS, Cardiac MRI for the Assessment of Cardioembolic Sources in Ischemic Stroke Study; CE, cardioembolic stroke; cv, cardiovascular; EF, ejection fraction; LAA, large artery atherosclerosis; LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; NRF, no relevant findings; PFO, patent foramen ovale; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; and WGA, wall motion abnormalities.

*Number of segments.

foramen ovale—even in combination with an atrial septum aneurysm—or an atrial septum defect is considered to be a low or uncertain risk source of embolism,[24] this is a limitation of cvMRI in practice. Notwithstanding of increased spatial and temporal resolution, the difficulty of stroke patients to perform a Valsalva maneuver during MRI immediately after application of contrast agent is important in this regard.

Taken together, corresponding findings according to both imaging modalities were present in 80 of 93 study patients with otherwise cryptogenic stroke (Table 3), resulting in a substantially lower degree of agreement (κ=0.24) than hypothesized. The observed differences in CaMRISS were mainly caused by the—to some extent—limited ability of stroke patients to complete the cvMRI examination and the—to some extent—limited availability of the MRI facility. Restricting the analysis to 79 cryptogenic stroke patients completing both cvMRI and TEE, the degree of agreement between both imaging modalities was moderate, indicating that cvMRI and TEE have different strengths and shortcomings.

In CaMRISS, the proportion of cryptogenic stroke patients (despite a standardized work-up, including echocardiography) at hospital discharge was reduced by 6% by using an additional cvMRI (Table 3). Subsequently, the secondary hypothesis of CaMRISS was not confirmed. However, excluding TEE/TTE findings in the CaMRISS cohort would have led to an almost 10% reduction of cryptogenic strokes according to cvMRI findings. With regard to the comparably high stroke recurrence rate after cryptogenic stroke,[3] additional cvMRI seems to have the potential to extend the diagnostic information, despite the fact that some detected low-risk sources of embolism may not result in subsequent adjustments of medical secondary stroke prevention. During the in-hospital stay, cvMRI findings resulted in evidence-based changes in medical secondary stroke prevention in 6% of all study patients with cryptogenic stroke according to standard diagnostic care, including echocardiography. Therefore, our results do not support routine use of cvMRI in hospitalized stroke patients who previously underwent TEE and TTE. MRI or other testing to assess for silent CAD might be performed in selected patients a certain time after stroke.

Besides feasibility and diagnostic value, timing and cost-effectiveness are major considerations for diagnostic imaging. cvMRI may be cost-effective if available 24/7, replacing echocardiography (in a subset of stroke patients undergoing brain MRI and the complete cvMRI examination) and subsequently shortening the in-hospital stay after acute ischemic stroke. In addition, MRI is able to identify atrial cardio(myo)pathy[28]—a so far neglected source of cardiac embolism. Furthermore, cvMRI is also able to precisely characterize left atrial enlargement[17]—independently associated with AF detection by an insertable cardiac monitor according to a recent study enrolling patients with cryptogenic stroke[29]—and the morphology of the left atrial appendage, another potential source of embolism (independent of AF). Because the exclusion of cardiac sources of stroke by using either TTE or TEE is a prerequisite of the present ESUS (Embolic Stroke of Undetermined Source) classification,[3] cardiac (magnetic resonance) imaging in the acute phase of stroke will be valuable even in case of a benefit of long-term non–vitamin K dependent oral anticoagulant therapy in ESUS patients.

CaMRISS has several weaknesses. First, not all patients underwent TTE in addition to TEE, but this reflects clinical routine.[9] Second, ischemic stroke is a heterogeneous disease and not all study patients remained cryptogenic according to routine diagnostic work-up. Third, cvMRI had to be interrupted in a few patients because of limited MRI capacity; however, this is also reflecting the clinical situation in a university hospital. In addition, cvMRI is not available in all stroke centers (so far), and only stroke patients able to follow breath-hold instructions can undergo cvMRI, further limiting the feasibility of the chosen approach. Fourth, since the ability to undergo TEE was an inclusion criterion of the CaMRISS study, we enrolled only stroke patients with an appointment to undergo TEE. Subsequently, cvMRI was done later than TEE in the majority of study patients. Fifth, although excellent inter- and intraobserver agreement was demonstrated by the cardiac MRI core laboratory in Essen, Germany,[30] this assessment was not part of the CaMRISS protocol. Finally, the definitive risk of recurrent stroke in stroke patients with extended transmural myocardial scarring and subsequent hypo- or akinesia in ≥3 wall segments has to be assessed in a large prospective trial.

Summary

Demonstrating feasibility and safety of cvMRI after acute ischemic stroke, CaMRISS failed to demonstrate a similar diagnostic value of cvMRI and TEE in the detection of cardioaortic embolic sources of stroke. However, cvMRI seems to have a complementary diagnostic information to TEE/TTE in patients with cryptogenic stroke by providing substantial information on undetected myocardial infarction, which was found in every eighth patient with acute ischemic stroke. Therefore, cvMRI may provide important contributions in the comprehensive assessment of the global cardiovascular risk of patients with acute ischemic stroke.

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Feasibility and Diagnostic Value of Cardiovascular Magnetic Resonance Imaging After Acute Ischemic Stroke of Undetermined Origin

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SUPPLEMENTAL MATERIAL

Supporting materials - Methods

Between January 2011 to November 2013, more than 2,500 ischemic stroke patients were treated at the Stroke Unit, Charité, Campus Benjamin Franklin and about 600 of these stroke patients underwent echocardiography. A screening log was kept between March 2012 and November 2013 including 350 consecutive stroke patients scheduled for echocardiography by the responsible physicians who were independent of study conduct. Of these 350 patients, 59 (16.9%) were enrolled. Patients were excluded due to the following reasons: Substantial atherosclerosis (14%), atrial fibrillation (8%), other defined stroke etiology or acute infection (14%), inability to enroll patients within 48 hours after onset of symptoms by the study personnel or non-availability of MRI (16%), inability (11%) or unwillingness (4%) to give informed consent, impaired renal function (9%), arrival >48 hours after stroke onset (5%), or MRI contraindication (2%).

Echocardiography

A multiplane TEE probe (X7-2t TEE) on a iE33 (Philips; Eindhoven, Netherland) and a 2-D TTE probe (3S-RS) on a Vivid 7 (GE Healthcare; Chalfont St. Giles, United Kingdom) were used to acquire the images. We analyzed the cardiac chambers, the left atrial appendage, and the cardiac valves. Color-coded Doppler imaging was used to reveal potential left-to-right shunts at the atrial level, and patency of the foramen ovale was assessed with agitated saline and the Valsalva maneuver. The aortic arch was inspected upon retraction of the ultrasound probe. Intravenous midazolam was used for conscious sedation during TEE. In addition, local anesthesia of the pharynx was achieved by using lidocaine spray.

MRI analysis

Using a 3 Tesla MR scanner (Magnetom Tim Trio; Siemens AG, Erlangen, Germany) ECG gated images were acquired during breath hold using a phased array receiver coil (Body Matrix-coil#TATS; Siemens AG). The following sequences were applied: Brain MRI: T2*-weighted imaging; diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC); Fluid-attenuated inverse recovery (FLAIR); time-of-flight MR-Angiography (TOF MRA). cvMRI: Cine images of 3 long-axis as well as 14-18 short-axis views (slice thickness 4 mm, no gap) using an ECG-gated gradient echo sequence, anatomical images of left atrial appendage, atrial shunt detection during Valsalva maneuver (after injection of 1 ml Gadobutrol (Gadovist®; Bayer HealthCare, Leverkusen, Germany) at a concentration of 1 mmol/ml), and time-resolved angiography with interleaved stochastic trajectories (TWIST) of the aorta was performed. Approximately eight to ten minutes after i.v. administration of 0.15 mmol/kg bodyweight Gadobutrol, an inversion recovery gradient-echo sequence was acquired in corresponding long-axis and short-axis slices adjusting the inversion time to null normal myocardium.

Supplement Table I

Presence of late gadolinium enhancement (LGE) in 16 out of 89 CaMRISS patients undergoing cvMRI and application of contrast agent.

Sex	Age (years)	Known CAD	LGE	WMA*	Ischemia according to ECG	Troponin T (admission)
M	55	no	transmural	yes	no	17 ng/l
M	69	no	transmural	yes	no	normal
M	70	yes	transmural	yes	no	normal
M	78	no	transmural	yes	Loss anterior R-waves	25ng/l
M	61	no	transmural	yes	no	normal
M	63	no	transmural	yes	no	normal
F	79	no	transmural	yes	no	16 ng/l
M	83	no	subendocardial	no	no	35 ng/l
M	52	no	subendocardial	no	no	normal
F	73	no	subendocardial	yes	Inferior Q waves	normal
M	71	no	subendocardial	no	no	normal
M	73	no	subendocardial	no	no	normal
M	52	yes	subendocardial	no	no	normal
M	62	no	subepicardially	no	no	25 ng/l
M	64	no	subepicardially	no	no	normal
M	31	no	subepicardially	no	no	normal

* wall motion abnormalities