

Prevalence of Myocardial Scar in Patients With Cryptogenic Cerebral Ischemic Events and Patent Foramen Ovale

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OBJECTIVES This study sought to evaluate the prevalence of subclinical myocardial infarctions with cardiovascular magnetic resonance imaging (CMRI) in patients with patent foramen ovale (PFO) after cryptogenic cerebral ischemic events.

BACKGROUND A thrombotic mass passing a PFO may embolize in cerebral but also in coronary arteries, resulting in both cerebral and myocardial ischemic events. CMRI with late gadolinium enhancement (LGE) analysis is the most sensitive imaging technique to detect small myocardial infarctions.

METHODS PFO patients ($n = 74$) with a first cryptogenic cerebral ischemic event without a clinical history for myocardial infarction underwent CMRI and coronary angiography. Right and left ventricular volumes and ejection fractions were measured by CMRI. LGE imaging was performed after administration of gadolinium-diethylenetriaminepentaacetic acid. The presence of atrial septal aneurysm (ASA) was evaluated by transesophageal echocardiography.

RESULTS LGE was detected in 8 of 74 (10.8%) patients. LGE pattern was transmural or subendocardial. Patients with LGE and those without did not differ in cardiovascular risk factors, type of ischemic event, presence of ASA, right and left ventricular volumes, and ejection fractions. LGE volume was small and comprised only $7.9 \pm 2.4\%$ of left ventricular muscle mass. Coronary artery disease was ruled out in 7 of 8 patients with LGE. There was a trend towards a larger PFO size in patients with LGE compared with patients without LGE (13.2 ± 4.1 mm vs. 16.0 ± 2.8 mm, $p = 0.06$).

CONCLUSIONS Subclinical myocardial infarctions determined in CMRI were observed in 10.8% of patients with PFO after a first cryptogenic cerebral ischemic event. Our results strengthen the pathophysiologic role of a PFO with paradoxical embolism in patients with cryptogenic cerebral ischemic events. (J Am Coll Cardiol Img 2010;3:833–9) © 2010 by the American College of Cardiology Foundation

There is an increasing use of percutaneous transcatheter device implantation for closure of patent foramen ovale (PFO) after cryptogenic ischemic events (1) although the pathophysiologic role of the PFO is controversial (2,3). According to the American Heart Association/American Stroke Association PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (4), not taking into account other noncerebral embolic events. Cerebral vessels are the main target of cardiac emboli. Nevertheless, other vessels such as

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coronary arteries may also be affected. The evidence of a thrombus in a PFO has been documented (5,6). In these rare cases, the thrombotic mass was extraordinary large. In the vast majority, there is no thrombus in a PFO of a patient with a cryptogenic cerebral ischemic event despite use of transesophageal echocardiography. The absence of a thrombus in PFO patients with cryptogenic ischemic events has often been used as an argument against the pathophysiologic role of a PFO with paradoxical embolism. However, a small thrombotic mass could easily pass the PFO without entrapment, leading to cerebral ischemic events. Entering the coronary arteries, the resulting small myocardial infarction (MI) could be subclinical or even asymptomatic. Cardiovascular magnetic resonance imaging (CMRI) with late gadolinium enhancement

(LGE) analysis is the most sensitive noninvasive imaging technique to detect even small MIs (7). The additional presence of a subclinical MI in the absence of coronary artery disease supports the hypothesis of paradoxical embolus as the underlying mechanism of cryptogenic stroke. The confirmation that a single patient has had 2 potential paradoxical embolic events, the combination of MI and stroke, would also support percutaneous closure of PFO by device implantation.

We evaluated the prevalence of MI with CMRI in patients after a first cryptogenic ischemic cerebral event and presence of a PFO.

METHODS

Seventy-four consecutive patients with a first cryptogenic ischemic cerebral event and PFO seen in transesophageal echocardiography without clinical

history of MI were included. Patients underwent CMRI study including LGE imaging for detection of MI. The cerebral ischemic event was classified as cryptogenic if other possible causes were excluded such as atherosclerotic stenoses or plaques of the carotid or vertebral arteries, aortal plaques, cardiac arrhythmias including atrial fibrillation or flutter, prothrombotic coagulation disorders, or cardiac thrombi. All patients underwent a diagnostic workup with 12-lead electrocardiography, Holter monitoring, Doppler sonography, transthoracic echocardiography, transesophageal echocardiography, and coagulation blood tests. Transesophageal echocardiography and CMRI were used to rule out intracardiac thrombi in both the atrial and ventricular chambers. Patients were scheduled for percutaneous closure of PFO based on the cryptogenic cerebral ischemic event in combination with the presence of an atrial septal aneurysm (ASA) or severe bubble passage seen in transesophageal echocardiography. All patients were in sinus rhythm, and there was no indication for oral anticoagulation due to other disorders. The study was approved by the local ethics committee, and all patients gave their written informed consent.

Transesophageal echocardiography. Transesophageal echocardiography for detection of PFO was performed with a multiplane, phased-array 4- to 7-MHz transesophageal echocardiography probe on an ATL HDI 5000 CV (Philips Medical Systems, Best, the Netherlands). For contrast enhancement, 10 ml of agitated hydroxyethyl starch solution was repeatedly administered into an antecubital vein with the patient performing proper Valsalva maneuver (8). Provokable right-to-left shunt was graded according to the amount of bubbles crossing the interatrial septum: no shunt = 0, mild shunt = 1 to 9 bubbles, moderate shunt = 10 to 20 bubbles, and severe shunt >20 bubbles or opacified left atrium due to bright contrast (9). The contrast agent was administered through a cubital vein. An ASA was defined as an excursion of the atrial septum >10 mm (10).

CMRI. CMRI was performed on a 1.5-T Intera CV whole-body MR Scanner (Philips Medical Systems). All data were acquired utilizing a dedicated 5-element cardiac phased-array coil. To determine left and right ventricular function, a retrospective ECG-gated segmented k-space balanced turbo field-echo sequence (steady-state free-precession [SSFP]) was used in short- and long-axis views along the true heart axis (11). Depending on the required field of view, the spatial resolution was

ABBREVIATIONS AND ACRONYMS

ASA = atrial septal aneurysm

CMRI = cardiovascular magnetic resonance imaging

Gd-DTPA = gadolinium-diethylenetriaminepentaacetic acid

LGE = late gadolinium enhancement

MI = myocardial infarction

PFO = patent foramen ovale

between 1.7×1.8 mm and 2.3×1.8 mm in-plane. Slice thickness was 10 mm. Echo time was 1.7 ms. Repetition time was 3.4 ms. Ten to 15 min after infusion of 0.2 mmol/kg body weight gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA, Magnevist, Schering, Germany), a LGE study using a 3D spoiled turbo gradient-echo sequence with a selective 180° inversion recovery pre-pulse was acquired in the short axis covering the whole left ventricle (20- to 22 5-mm slices). Two to 3 long-axis views with a similar 2D sequence were additionally performed. LGE was quantitatively assessed on a ViewForum Workstation with the Easy Vision Software Rel. 5.1 (Philips Medical Systems) (12).

Coronary angiography. Coronary angiography was performed in standard Judkins technique from the femoral approach using 5-F or 6-F catheters. For the right coronary artery, 2 to 3 projections and for the left coronary artery, 5 to 7 projections were performed after intracoronary administration of glycerol trinitrate. Exclusion of coronary artery disease was defined as a smooth vessel border without luminal stenoses or irregularities.

Statistical analysis. Categorical parameters are presented as counts and percentages. Comparison of proportions was done with chi-square test. Normal distribution for continuous variables were tested by use of the Kolmogorov-Smirnov test, and data are presented as mean \pm SD. Continuous variables for 2 groups were compared using the unpaired *t* test. A *p* value <0.05 was considered significant. Analyses were done with Statistica release 7.1 (StatSoft, Tulsa, Oklahoma).

RESULTS

LGE in CMRI was present in 8 of 74 (10.8%) patients. Patients with LGE as compared with patients without LGE did not differ in cardiovascular risk profile or type of cryptogenic cerebral ischemic event (Table 1). An ASA was present in 64% of the population, and its presence did not differ between patients with LGE and patients without LGE.

Severe bubble passage was present in 61 of 74 patients (82.4%) and was not different between groups. Severe bubble passage was seen in 7 of 8 (87.5%) patients with LGE in CMRI as compared with 54 of 66 (81.8%) patients without LGE (*p* = 0.69). PFO size in patients with severe bubble passage was statistically not different from patients without severe bubble passage (13.9 ± 4.1 mm vs. 11.8 ± 3.1 mm, *p* = 0.11). Patients with ASA had

Table 1. Patient Characteristics

	Total Population	Without LGE	With LGE	p Value
Patients	74	66	8	
Mean age (yrs)	45.9 \pm 13.4	45.2 \pm 13.0	51.8 \pm 16.2	0.17
Male, n	45 (60.8%)	40 (60.6%)	5 (62.5%)	0.92
Index event				
Stroke	60 (81.1%)	53 (80.3%)	7 (87.5%)	0.62
Transient ischemic attack	14 (18.9%)	13 (19.7%)	1 (12.5%)	
Cardiovascular risk factors				
Diabetes	3 (4.1%)	3 (4.5%)	0 (0.0%)	0.54
Hypertension	25 (33.8%)	22 (33.3%)	3 (37.5%)	0.82
Active smoker	16 (21.6%)	15 (22.7%)	1 (12.5%)	0.62
Hyperlipidemia	23 (31.1%)	21 (31.8%)	2 (25.0%)	0.69
Body mass index (kg/m ²)	25.8 \pm 3.9	25.9 \pm 4.0	25.2 \pm 2.7	0.84
PFO size, mm	13.4 \pm 4.0	13.2 \pm 4.1	16.0 \pm 2.8	0.06
Atrial septal aneurysm	47 (63.5%)	42 (63.6%)	5 (62.5%)	0.95
Coronary artery disease	5 (6.8%)	4 (6.1%)	1 (12.5%)	0.49

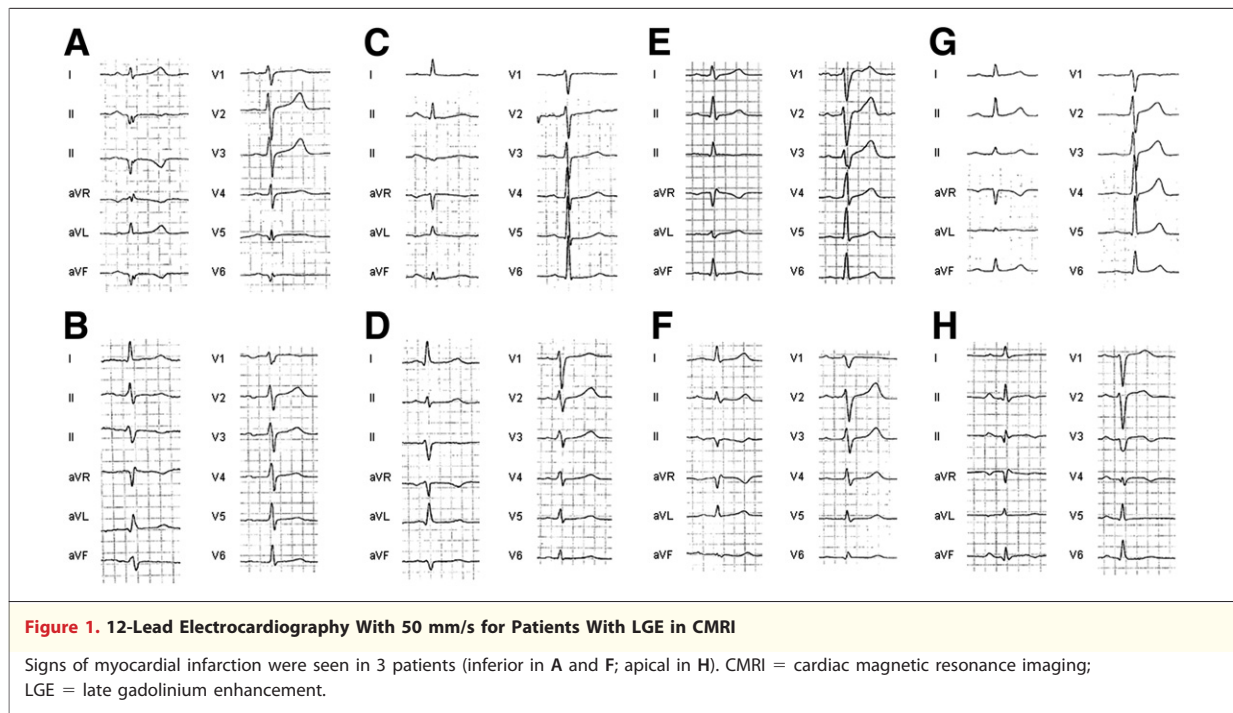
Values are n, mean \pm SD, or n (%).
 LGE = late gadolinium enhancement; PFO = patent foramen ovale.

a significantly larger PFO size (14.4 ± 3.9 mm) as compared with patients without ASA (12.0 ± 3.8 mm, *p* = 0.012). There was a trend towards a larger size of PFO in patients with LGE as compared to patients without LGE (16.0 ± 2.8 mm vs. 13.2 ± 4.1 mm, *p* = 0.06) (Table 1).

Signs of MI in 12-lead electrocardiography were present in 3 of 8 (37.5%) patients with LGE as detailed in Figure 1. In these 3 patients, the distribution of LGE was appropriate for the distribution of electrocardiogram's indication of MI. With coronary angiography, coronary artery disease was ruled in 7 of 8 (87.5%) patients with LGE. Values for LV and RV volume indices and ejection fractions were in normal range and did not differ between patients with or without LGE (Table 2). Pattern of LGE in CMRI was transmural or subendocardial (Fig. 2). LGE comprised $7.9 \pm 2.4\%$ (median 6.0%, range 2.4% to 17.7%) of left ventricular muscle mass.

DISCUSSION

In nonrandomized comparisons, the recurrence rate of stroke after transcatheter closure of PFO was lower compared with trials that used medical treatment (13). Nevertheless, with the lack of randomized data, the pathophysiologic role of PFO in cryptogenic stroke patients is controversially debated (2,3). We were able to demonstrate that LGE imaging using CMRI in those patients detects subclinical MI in about every tenth patient. The additional presence of a subclinical MI in the



absence of coronary artery disease supports the hypothesis of paradoxical embolus as the underlying mechanism of cryptogenic stroke.

MI as a consequence of paradoxical embolism via a PFO has been reported in some cases (14). In our population, MIs were predominantly small and did not affect LV volumes or ejection fraction, which were in normal range. The median LGE was 6.0% of left ventricular muscle mass. Amount of LGE was very limited compared with values for MIs due to coronary artery disease (12,15–18). The mainly small size of LGE also strengthens the hypothesis of paradoxical embolism of thrombotic material. A

small thrombotic mass can result in subclinical MI without evidence of thrombus in PFO even by use of transesophageal echocardiography.

The presence of LGE is not pathognomonic for MI. LGE has also been documented in different types of cardiomyopathy (19), myocarditis (19,20), and Takotsubo disease (21). In our population, LGE was transmural or subendocardial, which is the typical presentation of myocardial scar due to MI (20). In addition, coronary artery disease was ruled out in 7 of 8 patients by coronary angiography. Therefore, we interpret the presence of LGE as MI.

Multiple cerebral ischemic lesions on diffusion-weighted magnetic resonance imaging have been correlated to the presence of PFO seen in transesophageal echocardiography (22). In 106 patients with cryptogenic stroke, no difference was observed between patients with PFO as compared with patients without PFO. The frequency of multiple ischemic lesions on magnetic resonance imaging in relation to right-to-left shunting has been recently studied by Feurer et al. (23). Multiple ischemic lesions were seen in 23 of 165 (13.9%) patients with right-to-left shunt in comparison with 45 of 321 patients (14.0%) without right-to-left shunt ($p = 0.98$). In the subgroup of patients with cryptogenic stroke, there was a 3-fold higher frequency of multiple ischemic lesions in patients with right-to-left shunt (4 of 65, 6.2%) as compared with patients

Table 2. Cardiovascular Magnetic Resonance Imaging

	Total Population	Without LGE	With LGE	p Value
Left ventricular parameters				
LVEDVI (ml/m ² BSA)	71.2 ± 13.5	71.1 ± 13.5	72.6 ± 13.9	0.76
LVESVI (ml/m ² BSA)	23.4 ± 7.6	23.0 ± 7.2	26.5 ± 10.1	0.22
LVMMI (g/m ² BSA)	62.3 ± 10.1	61.9 ± 10.6	64.9 ± 5.3	0.44
LVEF (%)	67.7 ± 6.3	68.1 ± 5.7	64.4 ± 9.7	0.12
Right ventricular parameters				
RVEDVI (ml/m ² BSA)	79.2 ± 18.3	79.7 ± 18.4	74.5 ± 18.2	0.47
RVESVI (ml/m ² BSA)	29.0 ± 9.9	29.3 ± 10.1	26.5 ± 8.2	0.46
RVEF (%)	64.0 ± 5.6	63.9 ± 5.7	64.9 ± 4.6	0.63
Hemodynamic parameter				
Cardiac index (l/min/m ²)	3.1 ± 0.5	3.1 ± 0.5	3.4 ± 0.5	0.21
Measurements are mean ± SD. BSA = body surface area; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; LV = left ventricular; MMI = muscle mass index; RV = right ventricular.				

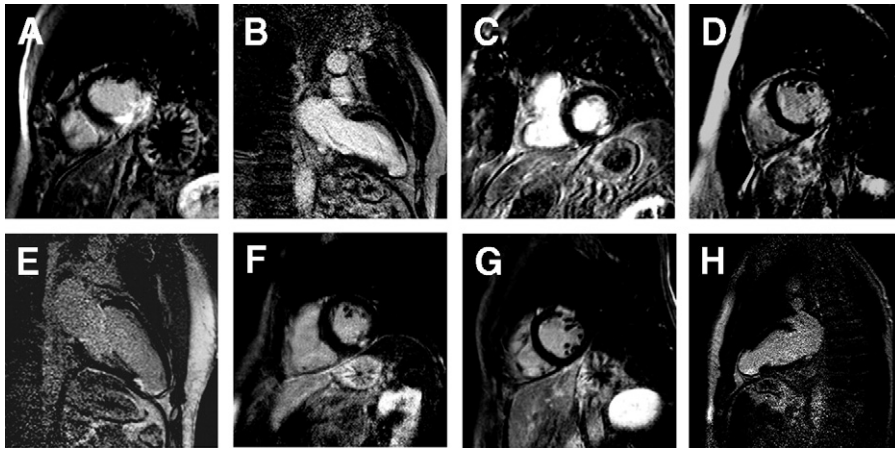


Figure 2. The Presence of LGE in CMRI

Panels correspond to those in Figure 1. The predominant circumscribed myocardial scars were subendocardial or transmural, and restricted to the supplying area of 1 coronary artery. LGE was located inferior in A, C, and F; apical in B, E, and H; inferolateral in D; and anterolateral in G. Abbreviations as in Figure 1.

without right-to-left shunt (2 of 86, 2.3%). The impact of an ASA in the context of multiple cerebral lesions has been evaluated by Bonati et al. (24). Multiple ischemic lesions in diffusion-weighted CMRI were significantly more frequent in cryptogenic stroke patients with PFO and ASA (16 of 30, 53%) versus patients with PFO without ASA (3 of 18, 17%; $p < 0.01$). This association remained significant after correction for PFO size, degree of right-to-left shunting, and vascular risk factors. In our study population, an ASA was present in 64% of patients. The presence of an ASA was not associated with a higher frequency of LGE in CMRI, but was associated with a strong trend towards a larger PFO size. This association was significant in the study by Bonati et al. (24). The presence of ASA has also been associated with a worse long-term prognosis with antiplatelet therapy (25), but not after percutaneous device implantation (26). Our population is pre-selected by the high frequency of ASA (64%), which has been reported for stroke patients in the range of 2% to 15% (27,28). The frequency of LGE in an unselected group of patients with cryptogenic ischemic cerebral events could be different from our presented results.

Recently, a lower atherosclerotic burden measured by carotid intima-media thickness was reported in patients with a cryptogenic cerebral ischemic event and PFO compared with patients without PFO (29). The authors concluded that a nonatherosclerotic mechanism may mediate the cerebrovascular event in the presence of PFO. We were able to extend this knowledge that in those

patients, MIs are detectable in about 10%. Crump et al. (30) did not find a difference in presence of PFO in 18 patients with MI and normal coronary angiograms as compared with 18 patients matched by age and sex. PFO prevalence was 28% in both groups and was presumably underdetected since contrast medium was injected immediately before exhalation, which does not meet the requirements of a proper Valsalva maneuver (8). Although use of transthoracic echocardiography allows an easier Valsalva maneuver, a full contrast of the right atrium in conjunction with a higher pressure necessary for opening a PFO is often missed due to the respiratory shift of the echocardiographic window.

On the basis of our data, we were not able to differentiate between a 1-step and a 2-step event. The trend for a larger PFO size in patients with myocardial scar may be a marker for a second event allowing a simpler passage of paradoxical emboli or otherwise a passage of a larger clot with following fragmentation. The fact that a single patient has had 2 potential paradoxical embolic events, the combination of MI and stroke, also supports percutaneous closure of PFO by device implantation.

Study limitations. There was no control group of cryptogenic stroke patients without PFO, and the number of patients studied was limited. We did not consider left atrial appendage flow velocity as a surrogate for potential left atrial appendage thrombus. However, left atrial appendage thrombus was excluded by transesophageal echocardiography. Furthermore, the population was pre-selected with a high frequency of ASA or presence of severe

bubble passage via PFO. Therefore, the 10.8% incidence of LGE in CMRI does not apply to a nonselected population with a first cryptogenic cerebral ischemic event. Nevertheless, the data strongly support a paradoxical embolism in the studied population in which a medical treatment strategy is favored according to present guidelines (4).

CONCLUSIONS

We were able to demonstrate using CMRI a 10.8% prevalence of subclinical MIs in patients with PFO

after a first cryptogenic cerebral ischemic event. Our results strengthen the pathophysiologic role of a PFO with paradoxical embolism in patients with cryptogenic cerebral ischemic events.

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