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ORIGINAL RESEARCH

High-Resolution Late Gadolinium Enhancement Magnetic Resonance for the Diagnosis of Myocardial Infarction With Nonobstructed Coronary Arteries

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ABSTRACT

OBJECTIVES The aim of this study was to assess the diagnostic yield of cardiac magnetic resonance (CMR) including high-resolution (HR) late gadolinium enhancement (LGE) imaging using a 3-dimensional respiratory-navigated method in patients with myocardial infarction with nonobstructed coronary arteries (MINOCA).

BACKGROUND CMR plays a pivotal role for the diagnosis of patients with MINOCA. However, the diagnosis remains inconclusive in a significant number of patients, the results of CMR being either negative or uncertain (i.e., compatible with multiple diagnoses).

METHODS Consecutive patients categorized as having MINOCA after blood testing, electrocardiography, coronary angiography, and echocardiography underwent conventional CMR, including cine, T2-weighted, first-pass perfusion, and conventional breath-held LGE imaging. HR LGE imaging using a free-breathing method allowing improved spatial resolution (voxel size 1.25 × 1.25 × 2.5 mm) was added to the protocol when the results of conventional CMR were inconclusive and was optional otherwise. Diagnoses retained after reviewing conventional CMR were compared with those retained after the addition of HR LGE imaging.

RESULTS From 2013 to 2016, 229 patients were included (mean age 56 ± 17 years, 45% women). HR LGE imaging was performed in 172 patients (75%). In this subpopulation, definite diagnoses were retained after conventional CMR in 86 patients (50%): infarction in 39 (23%), myocarditis in 32 (19%), takotsubo cardiomyopathy in 13 (8%), and other diagnoses in 2 (1%). In the remaining 86 patients (50%), results of CMR were inconclusive: negative in 54 (31%) and consistent with multiple diagnoses in 32 (19%). HR LGE imaging led to changes in final diagnosis in 45 patients (26%) and to a lower rate of inconclusive final diagnosis (29%) ($p < 0.001$). In particular, HR LGE imaging could reveal or ascertain the diagnosis of infarction in 14% and rule out the diagnosis of infarction in 12%. HR LGE imaging was particularly useful when the results of transthoracic echocardiography, ventriculography, and conventional CMR were negative, with a 48% rate of modified diagnosis in this subpopulation.

CONCLUSIONS HR LGE imaging has high diagnostic value in patients with MINOCA and inconclusive findings on conventional CMR. This has major diagnostic, prognostic, and therapeutic implications.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CMR = cardiac magnetic resonance

HR = high-resolution

LGE = late gadolinium enhancement

MINOCA = myocardial infarction with nonobstructed coronary arteries

TTE = transthoracic echocardiography

Patients with myocardial infarction with nonobstructed coronary arteries (MINOCA) represent a major diagnostic, prognostic, and therapeutic challenge in cardiology (1). Up to 5% to 10% of patients referred for coronary angiography for suspected myocardial infarction show no evidence of obstructive coronary artery disease (CAD) (2). The term "MINOCA" has been introduced as a "working diagnosis," given the multiple underlying mechanisms that can lead to such presentation. These include ischemic injuries secondary to type 1 or type 2 acute myocardial infarction (3), as well as takotsubo cardiomyopathy and acute myocarditis. The clinical management and prognosis being highly different according to the underlying etiology, dedicated diagnostic work-up is recommended (1). In this context, cardiac magnetic resonance (CMR) plays a pivotal role (4). Among other methods, late gadolinium enhancement (LGE) imaging is critical, the final diagnosis being based largely on the detection and assessment of the transmural distribution of myocardial injuries (5). However, in a substantial number of patients, the underlying etiology remains uncertain after CMR, the results of which are either negative or compatible with multiple diagnoses (2,6,7). Because patients with negative results on CMR have lower troponin values (8,9), we hypothesized that a major limitation of CMR is its spatial resolution, insufficient to detect small areas of myonecrosis. Free-breathing LGE imaging was recently introduced for high-resolution (HR) imaging of the left atrial wall (10). It has also been shown valuable in providing a detailed 3-dimensional architecture of ventricular scars to guide catheter ablation for ventricular arrhythmia (11). Using this method, spatial resolution is improved, with voxel size decreased by 4-fold compared with conventional breath-held methods. The aim of the present study was to assess the diagnostic yield of CMR including HR LGE imaging in patients presenting with MINOCA.

METHODS

POPULATION AND STUDY DESIGN. From January 2013 to March 2016, consecutive patients referred to the University Hospital of Bordeaux for the management of MINOCA were prospectively recruited. The pre-inclusion diagnostic work-up comprised blood testing including cardiac troponin, C-reactive protein, and leukocyte count; electrocardiography; coronary angiography; and transthoracic echocardiography (TTE). Inclusion criteria were in line with the recent European Society of Cardiology position paper defining MINOCA (1): 1) criteria for acute myocardial infarction including troponin rise above the 99th percentile upper reference limit and corroborative clinical evidence of infarction according to the fourth universal definition of myocardial infarction (4); 2) absence of obstructive CAD (≥50% stenosis) on coronary angiography; and 3) no clinically overt specific cause for the acute presentation. Patients diagnosed with clinically suspected myocarditis according to the European Society of Cardiology 2013 myocarditis task force (12) were not considered for inclusion. Exclusion criteria were contraindications to CMR, including patients with implantable cardioverter-defibrillators, and history of acute coronary syndrome associated with troponin rise. All patients underwent conventional CMR including LGE imaging using usual breath-held methods. Free-breathing HR LGE imaging was systematically added to the protocol in patients with inconclusive findings after conventional CMR and was optional otherwise, depending on the clinical work flow.

CMR ACQUISITION. Studies were performed on a 1.5-T system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) equipped with a 32-channel cardiac coil. The protocol comprised cine, T2-weighted, and first-pass perfusion imaging, as well as conventional LGE imaging performed 10 min post-contrast using 2 breath-held methods in 3 stacks of contiguous slices encompassing the whole ventricles in short-axis, 2-chamber, and 4-chamber orientations. The first method was a 3-dimensional inversion recovery-prepared turbo fast low-angle shot sequence (voxel size 1.8 × 1.4 × 6 mm) and the second a 2-dimensional phase-sensitive inversion recovery sequence (pixel size 1.8 × 1.3 mm, thickness 6 mm). Conventional CMR findings were reviewed in real time during the CMR study by a single reader (15 years' experience in CMR). Free-breathing HR LGE

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.

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TABLE 1 Baseline Characteristics (N = 229)

Age (yrs)	56 ± 17
Female	104 (45)
History of cardiac disorder	21 (9)
If so which diagnosis	
Atrial fibrillation	11 (6)
Valvular heart disease	4 (2)
Treated ventricular septal defect	2 (1)
Dilated cardiomyopathy	1 (0.4)
Left bundle branch block	1 (0.4)
Long-QT syndrome	1 (0.4)
Atrioventricular block	1 (0.4)
CAD risk factors	
Hypertension	69 (30)
Smoking	85 (37)
Diabetes mellitus	21 (9)
Hyperlipidemia	65 (28)
Overweight (BMI 25–29.9 kg/m^2)	107 (47)
BMI (kg/m^2)	25.7 ± 5.2
Family history of premature CAD	35 (15)
Clinical presentation	
Typical angina	119 (52)
Atypical chest pain	101 (44)
Pericarditis-like chest pain	9 (4)
Recent history of chest pain	37 (16)
Infection (within the preceding 30 days)	59 (26)
Emotional stress	17 (7)
Dyspnea	30 (13)
Palpitation	17 (7)
Fever	7 (3)
Light-headedness	37 (16)
Syncope	7 (3)
Biological tests	
Troponin (peak/normal)	35 (10–120)
CRP (mg/l)	2.9 (0.2–23.0)
Elevated C-reactive protein (>5 mg/l)	95 (42)
High leukocyte count	70 (31)
ECG at presentation	
STEMI	85 (37)
Sinus rhythm	222 (97)
LBBB	8 (4)
RBBB	10 (4)
Transthoracic echocardiography	
LVEF (%)	57 ± 7
Normal results	124 (54)
Regional WMA	90 (39)
Diffuse WMA	41 (18)
Pericardial effusion	6 (3)
Other finding	6 (3)
Coronary angiography	
Radiographic angiography	222 (97)
Coronary CTA	7 (3)
Normal coronary arteries	125 (55)
Non-obstructive CAD	104 (45)
Abnormal ventriculography*	70 (40)

Values are mean ± SD, n (%), or median (interquartile range). *Data not available in 56 (24%) patients.

BMI = body mass index; CAD = coronary artery disease; CRP = C-reactive protein; CTA = computed tomographic angiography; ECG = electrocardiography; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; RBBB = right bundle branch block; STEMI = ST-segment elevation myocardial infarction; TTE = transthoracic echocardiography; WMA = wall motion abnormality.

Continued in the next column

imaging was systematically added to the protocol in patients with inconclusive findings after conventional CMR and was optional otherwise, depending on the clinical work flow. In patients eligible for HR LGE imaging, an additional inversion time scout scan was performed after conventional LGE imaging, hence 15 to 20 min after contrast injection. HR LGE imaging was then performed using a 3-dimensional, inversion recovery-prepared, electrocardiographically gated, respiration-navigated gradient-echo pulse sequence with fat saturation (voxel size 1.25 × 1.25 × 2.5 mm, acquisition time 8 to 12 min depending on heart rate and breath rate) (9). Detailed protocols and sequence parameters are provided in the Supplemental Appendix.

CMR ANALYSIS AND INTERPRETATION. CMR interpretation was performed retrospectively, after the completion of patient inclusion. Two readers (with 5 and 15 years' experience in CMR) analyzed all conventional CMR studies in a random order. This interpretation was performed months or years after the CMR study, and the readers were blinded to the initial CMR report. Thus, the interpretation of conventional CMR images was truly blinded to the 3-dimensional HR LGE dataset, and the readers did not know whether HR LGE imaging had been subsequently performed. Then, the same readers analyzed again the entire population, this time adding HR LGE imaging to the conventional CMR analysis. In addition, a single reader (5 years' experience) read all studies twice in a random order to document intraobserver agreement. Left ventricular volumes and ejection fraction were quantified using Argus software (Siemens Medical Systems). Ventricular dilatation and systolic dysfunction were defined on the basis of previously reported normal values (13). Cine images were visually assessed to look for left ventricular or right ventricular wall motion abnormalities and pericardial effusion. T2-weighted images were analyzed to look for myocardial edema. Perfusion imaging was reviewed to look for perfusion defects at rest. LGE imaging was analyzed to look for myocardial or pericardial LGE. Conventional LGE images were

TABLE 2 Conventional CMR Findings in the Total Population (N = 229)

Chest pain to CMR delay (days)	4 (2–8)
Extracardiac findings	
Pulmonary infiltrate	6 (3)
Pleural effusion	9 (4)
Cine imaging	
Pericardial effusion	8 (4)
RVEF impairment	1 (0.4)
LVEF (%)	61 ± 9
LVEF impairment	48 (21)
LVEDVi (ml/m^2)	73 ± 18
Regional WMA	80 (35)
Rest perfusion*	
Perfusion defect	20 (13)
T2 imaging	
Myocardial T2w abnormality	95 (41)
Conventional LGE findings	
Negative	83 (36)
Definite myocardial LGE	129 (56)
Possible myocardial LGE	17 (7)
Ischemic LGE pattern	61 (27)
Nonischemic LGE pattern	69 (30)
Uncertain LGE pattern	16 (7)
Transmural LGE	30 (13)
LGE extent (number of segments)	1 (0–2)
Pericardial LGE	3 (1)
Post-conventional CMR diagnosis	
Definite diagnoses	138 (60)
AM	57 (25)
MI	56 (24)
TT	22 (10)
Other	3 (1)
Inconclusive diagnoses	91 (40)
Negative results on CMR	59 (26)
Either MI or AM	14 (6)
Either MI or TT	2 (1)
Either MI or negative	4 (2)
Either AM or negative	12 (5)

Values are median (IQR), n (%), or mean ± SD. *Data not available in 76 (33%) patients.

AM = acute myocarditis; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LVEDVi = left ventricular end-diastolic volume index; MI = myocardial infarction; RVEF = right ventricular ejection fraction; T2w = T2-weighted imaging; TT = takotsubo cardiomyopathy; other abbreviations as in Table 1.

reviewed in the 3 acquired orientations. The HR LGE imaging volume could be reviewed in multiplanar reformations of any orientation, depending on LGE location. For each sequence, magnification and windowing could be optimized by readers. To document potential uncertainty in the interpretation of LGE images, positive LGE findings were categorized as definite when the reader had no doubt in the interpretation and possible when the positivity of LGE was considered unclear. In each patient, the distribution of LGE was described as subendocardial, subepicardial, and/or midwall. LGE was considered transmural if involving the entire myocardial thickness in at least 1 location. In case of unclear transmural location, the LGE pattern was categorized as uncertain. The extent of LGE was quantified in numbers of segments involved, using the 17-segment American Heart Association model. The criterion to diagnose myocardial infarction on CMR was the presence of definite subendocardial or transmural LGE (14). The criterion to diagnose myocarditis was the presence of definite midwall and/or subepicardial LGE in the absence of subendocardial LGE (15). The criterion to diagnose takotsubo cardiomyopathy was either: 1) a wall motion abnormality involving the entire apical or basal levels in the absence of myocardial LGE (14); or 2) a similar wall motion abnormality documented on pre-inclusion ventriculography or TTE in a patient with normal wall motion and negative LGE on CMR. Results of CMR were categorized as conclusive when patients fulfilled the criteria for a definite diagnosis and as inconclusive otherwise: negative or uncertain CMR findings (possible LGE or definite LGE with an uncertain pattern, i.e., compatible with multiple diagnoses). Each reader established a first diagnosis on the basis of non-CMR diagnostic tests and conventional CMR only, blinded to the 3-dimensional HR LGE imaging. Patients with HR LGE were analyzed a second time, and a final diagnosis was established on the basis of non-CMR diagnostic tests and CMR including HR LGE imaging.

FOLLOW-UP. Patients with a final diagnosis of takotsubo cardiomyopathy underwent follow-up imaging using CMR or TTE at 3 months. Subsequent outcomes were analyzed in the subset of the population that could be practically followed at our institution (follow-up at 3 months and then every year). In case of recurrent acute coronary syndrome, the diagnosis of the episode was compared with the diagnosis retained after the initial MINOCA episode.

STATISTICAL ANALYSIS. The Shapiro-Wilk test of normality was used to assess whether quantitative data conformed to the normal distribution. Continuous data are expressed as mean ± SD when following a normal distribution and as median (interquartile range) otherwise. Categorical data are expressed as fraction (percentage). Nonweighted Cohen's kappa coefficients were used to analyze intra and interobserver agreement on the final diagnosis. Independent continuous variables were compared using independent-sample parametric (unpaired Student's

t-test or analysis of variance) or nonparametric (Mann-Whitney *U* test or Kruskal-Wallis test) tests depending on data normality. When differences were found among groups by using analysis of variance (or the Kruskal-Wallis test), the multiple-comparisons Tukey-Kramer method (or the Conover-Iman test) was used to compare all pairs of groups. Dependent continuous variables were compared using paired-sample parametric or nonparametric tests (paired Student's *t*-test, Wilcoxon signed rank test) depending on data normality. Independent categorical variables were compared using the chi-square test when expected frequencies were ≥5 and the Fisher exact test when they were <5. When a difference was found by testing multiple (>2) categorical samples, the Marascuillo procedure was used to compare all pairs of groups. Dependent categorical variables were compared using the paired-sample McNemar test. All statistical tests were 2-tailed. A p value <0.05 was considered to indicate statistical significance. Analyses were performed using NCSS 8 (NCSS Statistical Software, Kaysville, Utah).

RESULTS

POPULATION. A total of 229 patients presenting with MINOCA were recruited (mean age 56 ± 17 years, 45% women). The characteristics of the studied population are shown in Table 1. The median troponin increase was 35 times the upper limit of normal (interquartile range: 10 to 120 times). Electrocardiography showed ST-segment elevation myocardial infarction in 85 patients (37%). Results of TTE were negative in 124 patients (54%) and showed diffuse and regional wall motion abnormalities in 41 (18%) and 90 (39%), respectively. Coronary angiography showed normal arteries in 125 patients (55%) and nonobstructive CAD in 104 (45%). All patients underwent CMR including cine imaging, T2-weighted imaging, and LGE imaging using breath-held methods. First-pass perfusion imaging at rest was not available in 76 patients (33%). The delay between the onset of chest pain and the CMR study was 4 days (interquartile range: 2 to 8 days). Conventional CMR findings in the total population are listed in Table 2. Examples of definite diagnoses of acute myocardial infarction, acute myocarditis, and takotsubo cardiomyopathy are shown in Supplemental Figures 1 to 3, respectively.

POPULATION STUDIED WITH HR LGE IMAGING. HR LGE imaging was added to the protocol when the diagnosis remained inconclusive after conventional LGE imaging and was optional otherwise. A total of 5 patients with negative findings on conventional CMR did not complete HR LGE imaging, because of poor tolerance during CMR. In total, HR LGE imaging was performed in 172 patients (75%). The characteristics of patients with (n = 172) and without (n = 57) HR LGE are compared in Supplemental Table 1. The population with additional HR LGE imaging was, as expected, more likely to show uncertain diagnosis after conventional CMR (50% vs. 9%; p < 0.001). In addition, the troponin peak and the rate of elevated C-reactive protein were lower (p < 0.001 and p = 0.02, respectively), and results of TTE and ventriculography more frequently negative (p = 0.03 and p = 0.02, respectively).

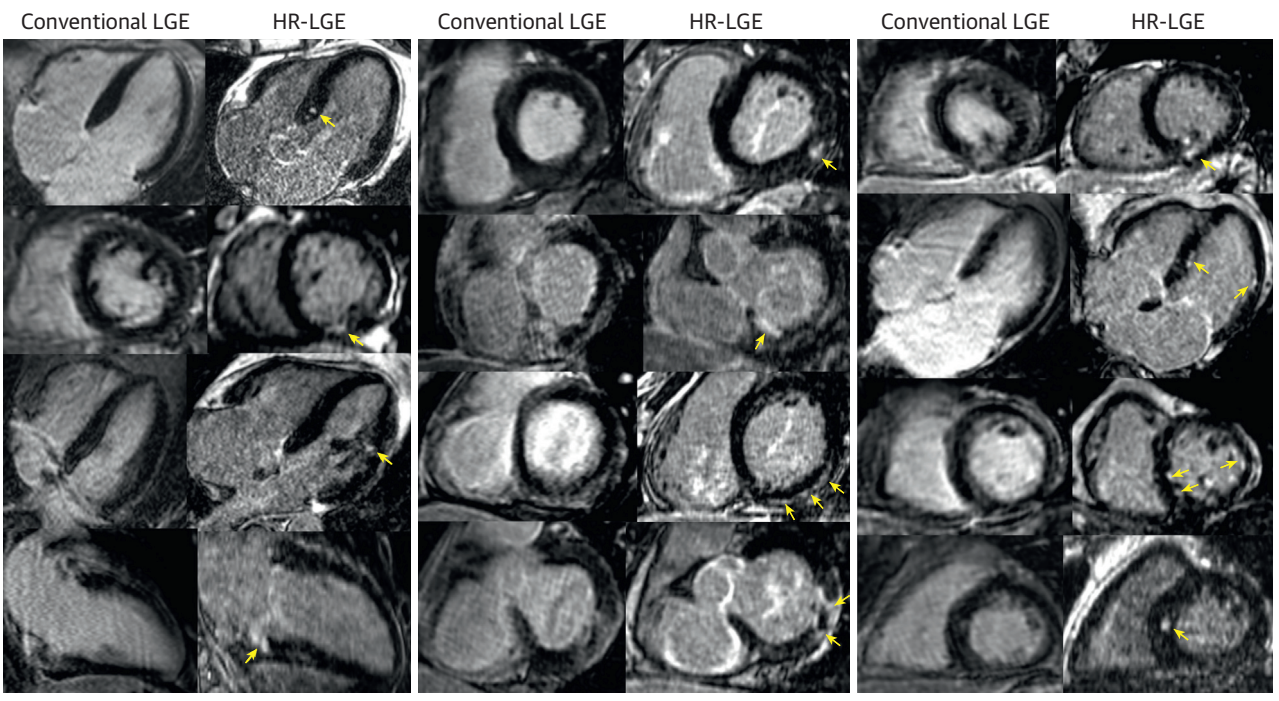
CONVENTIONAL VERSUS HR LGE FINDINGS. After reviewing conventional CMR findings in this subpopulation (n = 172), definite diagnoses could be retained in 86 patients (50%), including myocardial infarction in 39 (23%), acute myocarditis in 32 (19%), takotsubo cardiomyopathy in 13 (8%), and other diagnoses in 2 (1%; hypertrophic cardiomyopathy and endomyocardial fibrosis). In the remaining 86 patients (50%), results of conventional CMR were inconclusive: negative in 54 (31%) and consistent with multiple diagnoses (infarction or myocarditis in 14 [8%], myocarditis or negative results in 12 [7%],

TABLE 3 LGE Findings and Final Diagnosis Before and After HR LGE Imaging

	Conventional LGE Imaging Only	Conventional and HR LGE Imaging	p Value
LGE characteristics			
Negative myocardial LGE	68 (39)	61 (35)	0.143
Definite myocardial LGE	87 (51)	110 (64)	<0.001
Possible myocardial LGE	17 (10)	1 (1)	<0.001
Ischemic LGE pattern	45 (26)	63 (37)	<0.001
Nonischemic LGE pattern	44 (26)	47 (27)	0.629
Uncertain LGE pattern	15 (9)	1 (1)	<0.001
Transmural LGE	17 (10)	19 (11)	0.754
LGE extent (number of segments)	1 (0–2)	1 (0–2)	0.011
Pericardial LGE	3 (2)	5 (3)	0.625
Post-CMR diagnosis			
Definite diagnoses	86 (50)	122 (71)	<0.001
AM	32 (19)	46 (27)	0.002
MI	39 (23)	62 (36)	<0.001
TT	13 (8)	13 (8)	0.999
Others	2 (1)	1 (1)	0.999
Inconclusive diagnoses	86 (50)	50 (29)	<0.001
Negative results on CMR	54 (31)	48 (28)	0.211
Either MI or AM	14 (8)	1 (1)	0.001
Either MI or TT	2 (1)	0 (0)	0.480
Either MI or negative	4 (2)	0 (0)	0.134
Either AM or negative	12 (7)	1 (1)	0.003

Values are n (%) or median (interquartile range).
HR = high-resolution; other abbreviations as in Tables 1 and 2.

FIGURE 1 Comparison Between Conventional and HR LGE Images in Patients With MINOCA

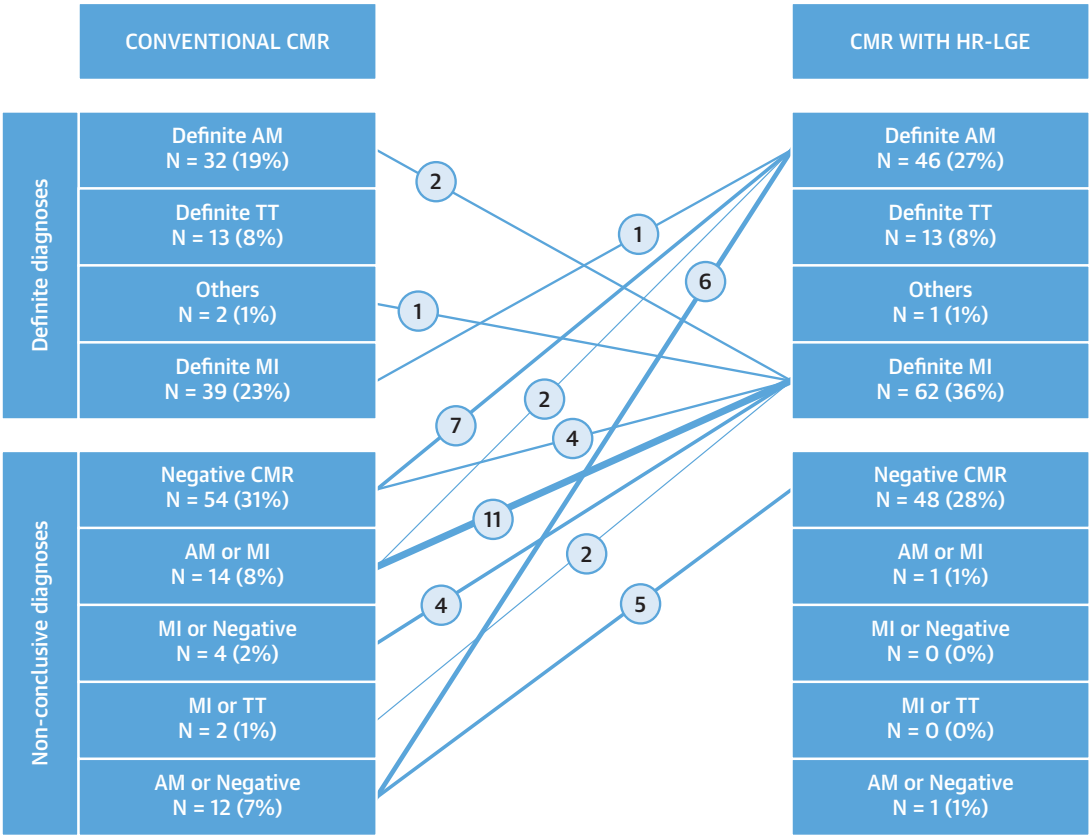


Late gadolinium enhancement (LGE) images from conventional breath-held **(left columns)** and free-breathing LGE at higher spatial resolution (high-resolution [HR] LGE imaging) **(right columns)** are provided for 12 patients. In all, the addition of HR LGE imaging led to a modification of the final diagnosis, either because of improved detection of myocardial injuries or because of improved assessment of LGE transmural location. **Arrows** indicate sites of LGE.

infarction or negative results in 4 [2%], and infarction or takotsubo cardiomyopathy in 2 [1%]). CMR results before and after reviewing HR LGE imaging are compared in Table 3. The rate of definite myocardial LGE was higher on HR LGE imaging than on conventional LGE (64% vs. 51%; $p < 0.001$). Likewise, the rate of uncertain LGE transmural location was lower on HR LGE imaging (1% vs. 15%; $p < 0.001$). Comparisons between conventional and HR LGE images are shown in Figure 1. The interpretation of myocardial injuries derived from HR LGE imaging led to a modification of the diagnosis in 45 of 172 patients (26%). Diagnostic changes before and after the addition of HR LGE imaging are shown in the Central Illustration. Most diagnostic changes (41 of 45 [91%]) occurred in patients with inconclusive diagnoses after conventional CMR. After the addition of HR LGE imaging, the rate of inconclusive CMR decreased from 86 to 50 of 172 (50% vs. 29%; $p < 0.001$). Likewise, the number of patients with definite diagnoses of myocardial infarction and myocarditis increased ($p < 0.001$ and $p = 0.002$, respectively). In particular, the addition of HR LGE imaging could reveal or ascertain myocardial infarction in 24 patients (14%). In these patients, conventional CMR findings had been interpreted as negative in 4, compatible with multiple diagnoses in 17, and suggestive of different diagnoses in 3 (2 as definite myocarditis, and 1 as hypertrophic cardiomyopathy, in whom HR LGE imaging showed definite infarction). In addition, HR LGE imaging could rule out the diagnosis of myocardial infarction in 21 patients (12%). In these patients, conventional CMR findings had been interpreted as negative in 7, compatible with multiple diagnoses including infarction in 13, and as definitely suggestive of infarction in 1 (interpreted as definite myocarditis after HR LGE imaging).

CHARACTERISTICS OF PATIENTS BENEFITING FROM HR LGE IMAGING. In a total of 40 patients, definite diagnoses was introduced after reviewing HR LGE images, while conventional CMR results were inconclusive or suggestive other diagnoses. The characteristics of these patients benefiting from HR LGE

CENTRAL ILLUSTRATION **Diagnostic Changes Introduced by HR LGE Imaging (172 Patients With Both Conventional CMR and HR LGE Imaging)**



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The diagnoses retained after conventional cardiac magnetic resonance (CMR) methods and after the addition of HR LGE imaging are shown in the **left and right columns**, respectively. **Connecting lines** indicate diagnostic changes, the number of patients concerned being overlaid on each line. AM = acute myocarditis; HR = high-resolution; LGE = late gadolinium enhancement; MI = acute myocardial infarction; TT = takotsubo cardiomyopathy.

imaging are analyzed in Table 4. They more frequently had negative findings on TTE, ventriculography, and cine magnetic resonance ($p = 0.01$, $p = 0.02$, and $p = 0.04$, respectively), and the pattern of hyperenhancement on conventional LGE imaging was more frequently uncertain ($p < 0.001$). The diagnosis after conventional CMR was more often negative or uncertain ($p < 0.001$) and less often consistent with myocarditis, infarction, or takotsubo cardiomyopathy ($p = 0.01$, $p < 0.001$, and $p = 0.04$, respectively). Examples of definite diagnoses introduced thanks to the addition of HR LGE imaging are shown in Figures 2 to 4.

INTRAOBSERVER AND INTEROBSERVER AGREEMENT ON FINAL DIAGNOSIS. Agreement on final diagnosis after conventional CMR and after HR LGE imaging is listed in Table 5. Intra- and interobserver agreement on final diagnosis was excellent for both conventional CMR and HR LGE imaging. Intraobserver agreement was significantly higher than interobserver agreement ($p < 0.05$ for both conventional CMR and HR LGE imaging). Intraobserver and interobserver agreement was higher after HR LGE imaging than after conventional CMR methods only, although the difference was not statistically significant ($p = NS$).

PATIENT CHARACTERISTICS ACCORDING TO FINAL DIAGNOSIS. Including all available information and in the total population, the final diagnoses were myocarditis in 71 of 229 (31%), myocardial infarction in 79 of 229 (34%), takotsubo cardiomyopathy in 22 of 229 (10%), negative results on CMR in 53 of 229 (23%),

TABLE 4 Characteristics of Patients Benefiting From HR LGE Imaging*

	HR LGE Imaging Does Not Introduce a New Definite Diagnosis (n = 132)	HR LGE Imaging Introduces a New Definite Diagnosis (n = 40)	p Value
Age (yrs)	57 ± 17	55 ± 17	0.503
Female	64 (48)	19 (48)	0.913
History of cardiac disorder	11 (8)	4 (10)	0.752
Number of CAD risk factors	1 (2-3)	1 (2-3)	0.600
Clinical presentation			
Typical angina	68 (52)	19 (48)	0.656
Atypical chest pain	57 (43)	20 (50)	0.447
Pericarditis-like chest pain	7 (5)	1 (3)	0.683
Recent history of angina	24 (18)	6 (15)	0.642
Infection (within the preceding 30 days)	27 (20)	12 (30)	0.207
Emotional stress	12 (9)	1 (3)	0.304
Dyspnea	16 (12)	4 (10)	0.999
Palpitation	10 (8)	2 (5)	0.735
Light-headedness or syncope	25 (19)	7 (18)	0.838
Laboratory findings			
Troponin (peak/normal)	27.3 (9.3–97.8)	30.3 (8.4–59.2)	0.080
Elevated C-reactive protein (>5 mg/l)	51 (39)	13 (33)	0.482
High leukocyte count (>10 g/l)	40 (30)	11 (28)	0.734
ECG at presentation			
STEMI	48 (36)	13 (33)	0.655
Sinus rhythm	129 (98)	40 (100)	0.999
LBBB or RBBB	9 (7)	3 (8)	0.999
Transthoracic echocardiography			
LVEF (%)	57.0 ± 6.7	58.6 ± 5.6	0.169
Normal TTE	70 (53)	30 (75)	0.014
Regional WMA	56 (42)	6 (15)	0.002
Diffuse WMA	24 (18)	3 (8)	0.137
Coronary angiography			
Normal coronary arteries	76 (58)	23 (58)	0.993
Nonobstructive CAD	55 (42)	17 (42)	0.993
Abnormal ventriculography	39 (41)	6 (19)	0.025
Conventional CMR characteristics			
LVEF (%)	61.5 ± 9.2	64.0 ± 7.8	0.109
Regional WMA	49 (37)	8 (20)	0.044
Pericardial effusion	6 (5)	1 (3)	0.999
Myocardial T2w abnormality	52 (39)	14 (35)	0.663
Perfusion defect	12 (9)	3 (8)	0.999
Negative myocardial LGE	56 (42)	12 (30)	0.159
Definite myocardial LGE	70 (53)	17 (42)	0.242
Possible myocardial LGE	6 (5)	11 (28)	<0.001
Ischemic LGE pattern	39 (30)	6 (15)	0.067
Nonischemic LGE pattern	36 (27)	8 (20)	0.356
Uncertain LGE pattern	1 (1)	14 (35)	<0.001
Transmural LGE	5 (4)	2 (5)	0.665
LGE extent (number of segments)	1 (0–2)	1 (0–1)	0.500
Pericardial LGE	3 (2)	0 (0)	0.999

Continued on the next page

and uncertain results on CMR in 4 of 229 (2%). Patient characteristics according to final diagnosis are compared in Table 6.

PATIENT OUTCOMES. All 22 patients with definite diagnosis of takotsubo cardiomyopathy underwent follow-up imaging (CMR in 8, TTE in 14), revealing normalization of left ventricular wall motion in all cases. Clinical follow-up information could be retrieved for only 116 of 229 (51%), because other patients were not followed at our institution. The median follow-up duration was 2.9 years (interquartile range: 1.0 to 3.7 years). Adverse outcomes included rehospitalization in a cardiology department in 20 of 116 patients (17%), including 8 of 116 patients (7%) because of recurrence of acute coronary syndrome. In these 8 patients, initial diagnoses were infarction in 4, myocarditis in 3, and negative CMR findings in 1. These patients were also retained after recurrence, except for the patient with initial negative results on CMR, whose recurrence was attributed to myocardial infarction secondary to coronary vasospasm. Death occurred in 5 of 116 patients (4%), including 1 (1%) attributed to a cardiac cause (sudden cardiac arrest in a patient with initial diagnosis of myocardial infarction). The comparison of outcomes according to the final diagnosis retained after the initial MINOCA episode is shown in Table 7.

DISCUSSION

The present study is the first to introduce the use of free-breathing HR LGE imaging for the diagnostic work-up of MINOCA. Studying a series of 229 consecutive patients with MINOCA, including 172 using both conventional and free-breathing LGE methods, the results show that the addition of HR LGE imaging leads to a higher rate of definite myocardial LGE and a lower rate of LGE of uncertain transmural location. This translates into a change in final diagnosis in 26% of the patients undergoing both methods and a lower rate of inconclusive CMR. Most diagnostic changes occur in patients with negative or uncertain results on diagnostic work-up after TTE, ventriculography, and conventional CMR.

POPULATION CHARACTERISTICS AND CONVENTIONAL CMR FINDINGS. The inclusion criteria conformed to the definition of MINOCA (1). The demographics and risk factors of the population are consistent with prior large series of patients with MINOCA (2,16). Electrocardiographic findings are also consistent with prior reports on MINOCA, with <40% of patients exhibiting ST-segment elevation (2,17). Likewise, the rates of negative findings on TTE and nonobstructive CAD on angiography are in agreement with past studies (2,18,19). The conventional CMR protocol conformed to the guidelines of the Society for Cardiovascular Magnetic Resonance (20). The rate of negative findings on CMR and the distribution of etiologies in patients with positive CMR

are consistent with past CMR series in patients with MINOCA (2,5,6,8,21,22). Regarding CMR methods, our results confirm that LGE is the cornerstone of the etiologic diagnosis in patients with MINOCA, while cine, T2-weighted, and first-pass perfusion imaging often produce negative results. The limited sensitivity of T2 imaging in the present study may be explained by incomplete cardiac coverage or by the intrinsic limitations of T2-weighted imaging for the assessment of myocardial edema. The negative results on T2 and cine imaging may also be explained by the delay between the onset of chest pain and the CMR study. Most patients were studied within the first week, but myocardial edema is known to show dynamic changes over that period (23,24). Likewise, transient wall motion abnormalities secondary to ischemic myocardial stunning or stress-induced cardiomyopathy may last only a few days, and cine imaging performed several days after the episode may be less sensitive than TTE performed on day 1. This appeared to be quite common in our series, as 34% of the patients with negative CMR findings showed wall motion abnormalities on TTE at admission.

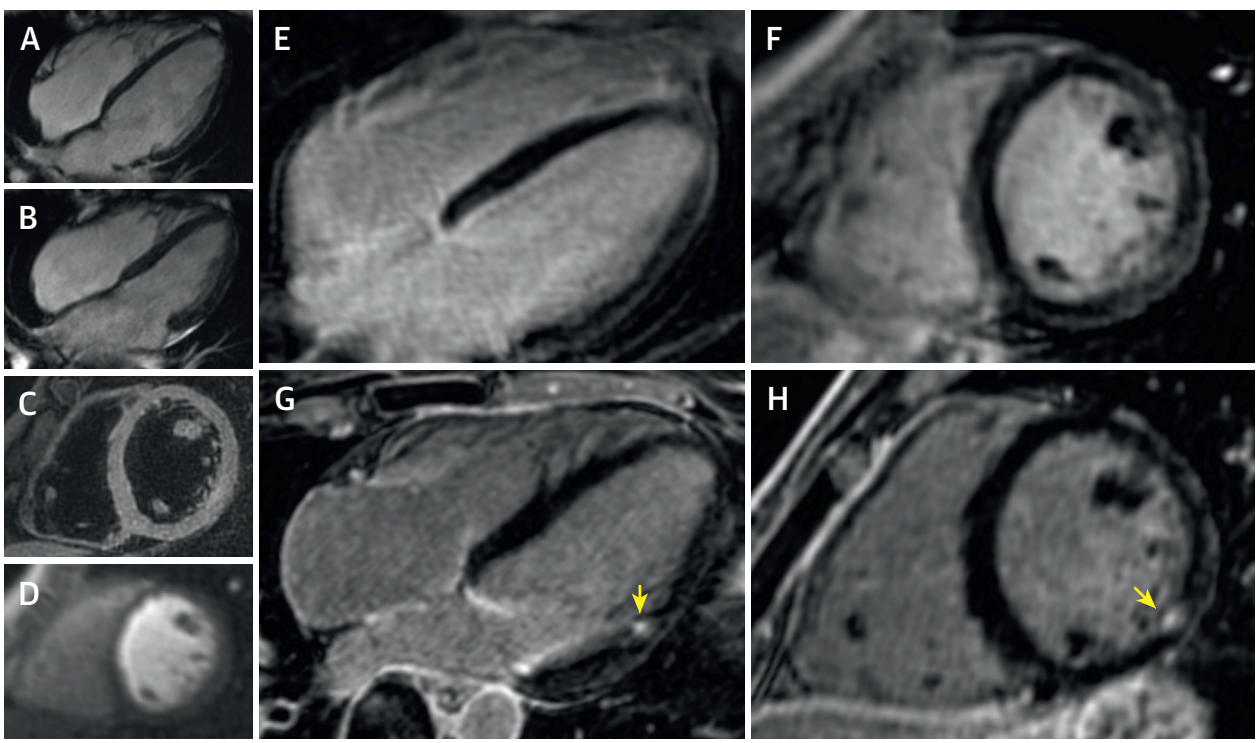
TABLE 4 Continued

	HR LGE Imaging Does Not Introduce a New Definite Diagnosis (n = 132)	HR LGE Imaging Introduces a New Definite Diagnosis (n = 40)	p Value
Conventional CMR diagnosis			
Negative or inconclusive results on CMR	50 (38)	36 (90)	<0.001
Definite myocarditis	30 (23)	2 (5)	0.010
Definite myocardial infarction	38 (29)	1 (3)	<0.001
Definite takotsubo cardiomyopathy	13 (10)	0 (0)	0.041
Other	1 (1)	1 (3)	0.412

Values are mean ± SD, n (%), or median (IQR). *Refers to patients with definite diagnoses introduced after reviewing HR LGE images while conventional CMR results were normal, inconclusive, or suggestive of another diagnosis.

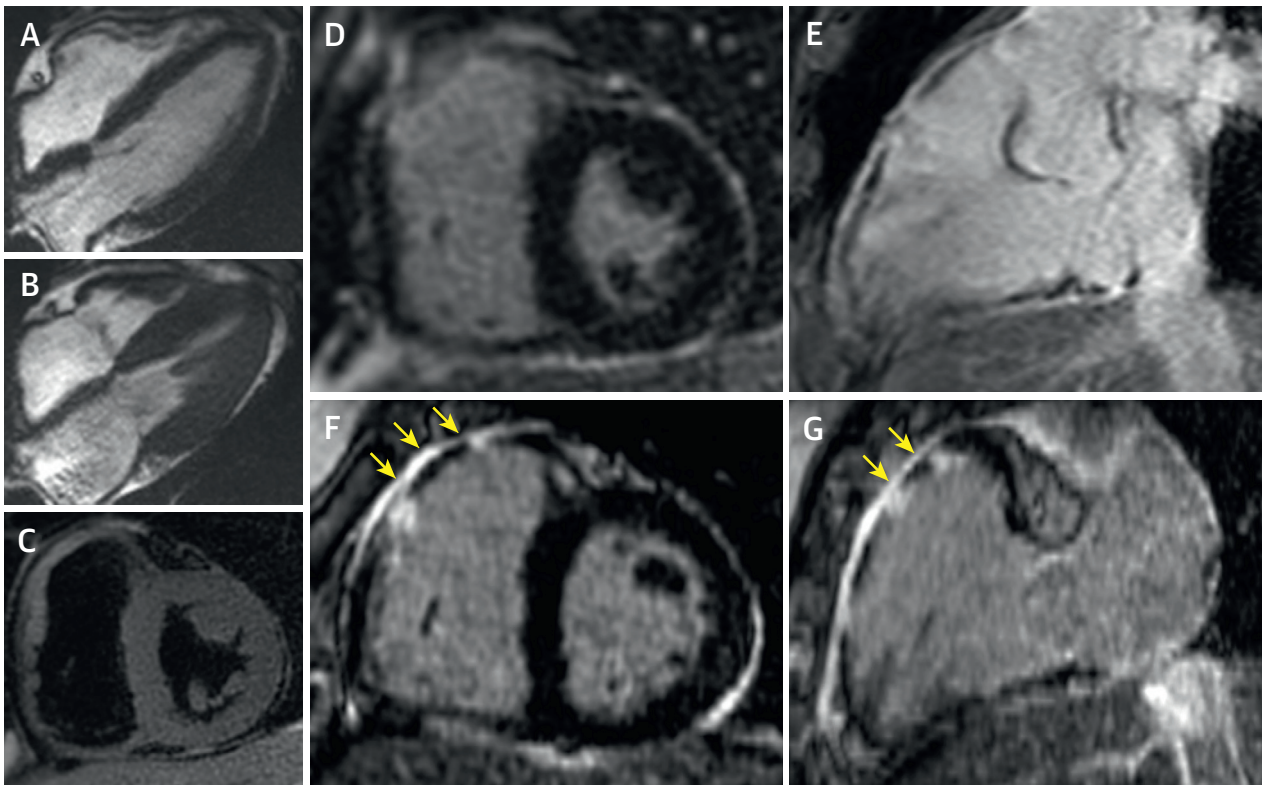
Abbreviations as in Tables 1 to 3.

FIGURE 2 A 33-Year-Old Woman Benefiting From HR LGE Imaging



The patient presented with typical angina and mild troponin rise. Results of electrocardiography, transthoracic echocardiography, and coronary angiography were normal. On cardiac magnetic resonance on day 2, results of cine (end-diastole **[A]** and end-systole **[B]**), T2-weighted **(C)**, first-pass rest perfusion **(D)**, and conventional LGE **(E,F)** imaging were considered negative. HR LGE showed focal subendocardial enhancement on the inferolatero mid segment, consistent with microinfarction **(arrows in G and H)**. Additional diagnostic work-up revealed no overt embolic cause on 24-h Holter monitoring, no biological substrate for thrombophilia, and no evidence of systemic vasculitis. Abbreviations as in Figure 1.

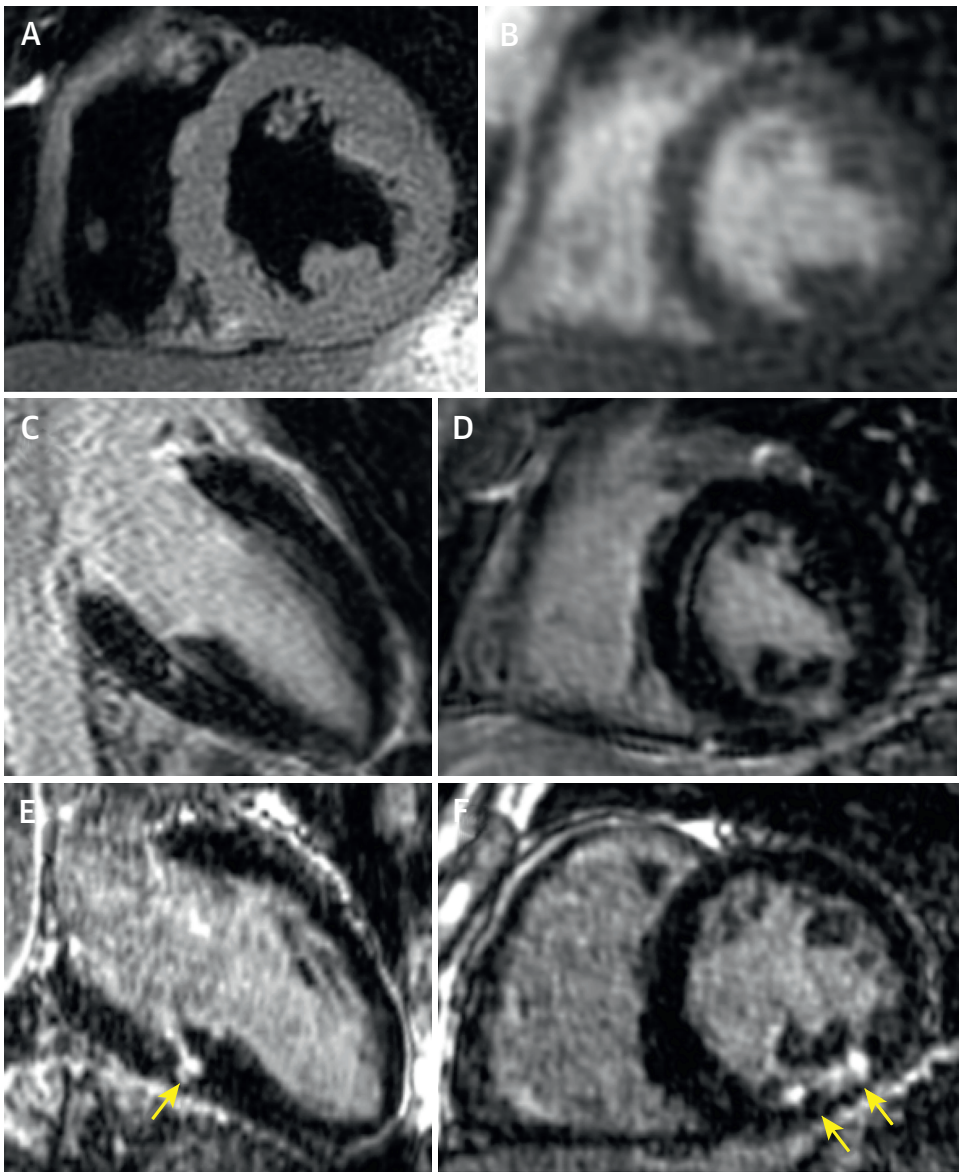
FIGURE 3 A 55-Year-Old Woman Benefiting From HR LGE Imaging



The patient presented with atypical chest pain, troponin increase, elevated C-reactive protein, and a high leukocyte count. Results of electrocardiography and transthoracic echocardiography were normal. Coronary angiography revealed nonobstructive coronary artery disease (CAD). On cardiac magnetic resonance performed on day 5, results of cine (end-diastole **[A]** and end-systole **[B]**), T2-weighted **(C)**, and conventional LGE **(D,E)** imaging were considered negative. HR LGE showed myocardial infarction in the right ventricular outflow tract area, with microvascular obstruction **(arrows in F and G)**. Given the presence of nonobstructive CAD, a mechanism of plaque disruption with spontaneous thrombus resorption was suspected. Abbreviations as in Figure 1.

HR LGE IMAGING FINDINGS. In line with prior studies, we found high rates of negative or uncertain findings after conventional CMR methods (2). Compared with conventional breath-held LGE methods, the amount of myocardium contained in each single voxel is decreased by 4-fold using HR LGE imaging (from 15.1 to 3.9 mm^3). The addition of HR LGE imaging led to a higher rate of definite myocardial LGE and a lower rate of LGE of uncertain transmural location. The detection of LGE and the accurate description of its transmural distribution are major determinants of CMR diagnosis (6,14) and are often a complex interpretation. When LGE is focally transmural, it may be difficult to distinguish between a subendocardial and a subepicardial primary location of the injury. Likewise, small subendocardial injuries may be missed because of poor contrast with the blood pool, while those adjacent to trabeculations or papillary muscles may be misinterpreted as of intramural location (25). Last, subepicardial LGE may be mistaken for epicardial fat or coronary vessels. The addition of HR LGE imaging translated into a change in final diagnosis in 26% of the patients undergoing both methods and a lower rate of inconclusive CMR. Of note, most diagnostic changes introduced by HR LGE imaging were due to improved diagnostic confidence rather than to the detection of new myocardial lesions undetected by conventional LGE imaging (two-thirds vs. one-third) (**Central Illustration**). This highlights the practical challenge of LGE interpretation in the context of MINOCA, in which myocardial injuries are smaller. Our results show that resolving these uncertainties has a significant impact on patient management. Particularly, HR LGE imaging could reveal or ascertain myocardial infarction in 14% and rule out myocardial infarction in 12%. Most diagnostic changes occurred in patients with inconclusive

FIGURE 4 A 60-Year-Old Man Benefiting From HR LGE Imaging



The patient presented with atypical chest pain and mild troponin increase. Results of electrocardiography, transthoracic echocardiography, coronary angiography, and ventriculography were normal. On cardiac magnetic resonance performed on day 5, results of cine, T2-weighted **(A)**, and rest perfusion **(B)** imaging were negative. On conventional LGE imaging, a focal enhancement was suspected on the inferomid segment, although categorized as uncertain **(C,D)**. HR LGE imaging showed definite subendocardial enhancement consistent with infarction **(E,F)**. Additional diagnostic work-up revealed no overt cause of myocardial infarction. Abbreviations as in Figure 1.

diagnosis after TTE, ventriculography, and conventional CMR. The rate of modified diagnosis was 41 of 86 (48%) in this subpopulation compared with 4 of 86 (5%) in those with definite diagnoses retained after conventional CMR methods. Thus, the implementation of HR LGE imaging in clinical practice should focus on these patients.

TABLE 5 Intraobserver and Interobserver Agreement on Final Diagnosis

	Low-Resolution LGE Imaging		High-Resolution LGE Imaging	
	(n = 229)	95% CI	(n = 172)	95% CI
Intraobserver agreement	κ = 0.978	0.953-1.000	κ = 0.992	0.976-1.000
Interobserver agreement	κ = 0.803	0.735-0.871	κ = 0.903	0.850-0.956

CI = confidence interval; LGE = late gadolinium enhancement.

TABLE 6 Characteristics According to Final CMR Diagnosis

	Negative CMR Results (n = 53)	Myocarditis (n = 71)	Myocardial Infarction (n = 79)	Takotsubo Cardiomyopathy (n = 22)	p Value
Age (yrs)	56 ± 16	48 ± 15	57 ± 17	72 ± 14	<0.001*†‡§‖
Female	54.7	28.2	40.5	90.9	<0.001*‡§‖
History of cardiac disorder	11.3	2.8	11.4	13.6	0.096
Number of CAD risk factors	2 (1-3)	2 (1-3)	2 (1-3)	3 (2-3)	0.037‡§
Clinical presentation					
Typical angina	39.6	50.7	67.1	31.8	0.003‖¶
Atypical chest pain	54.7	43.7	31.7	63.6	0.013‖¶
Pericarditis-like chest pain	5.7	5.6	1.3	4.6	0.371
Recent history of angina	18.9	18.3	16.5	0.0	0.124
Infection (within the preceding 30 days)	20.80	45.1	17.8	4.6	<0.001*§‖
Emotional stress	5.7	2.8	3.8	40.9	<0.001‡§‖
Dyspnea	18.9	11.3	7.6	22.7	0.124
Palpitation	9.4	5.6	5.1	18.2	0.179
Light-headedness or syncope	18.9	14.1	12.7	63.7	0.001§‖
Laboratory findings					
Troponin (peak/normal)	9.0 (4.8-18.0)	68.6 (20.0-212.8)	62.5 (18.0-141.7)	38.6 (24.6-75.5)	<0.001*¶
C-reactive protein value (mg/l)	12.4 ± 31.6	34.0 ± 45.9	13.1 ± 33.2	20.4 ± 31.3	<0.001*†
Elevated C-reactive protein (>5 mg/l)	26.4	63.4	29.1	45.5	<0.001*†
High leukocyte count (>10 g/l)	24.5	36.6	20.3	59.1	0.002‡‖
ECG at presentation					
STEMI	18.9	38.0	43.0	59.1	0.004‡¶
Sinus rhythm	94.3	98.6	98.7	95.5	0.368
Arrhythmia	5.7	1.4	1.3	4.6	0.368
LBBB or RBBB	7.6	2.8	10.1	9.1	0.349
Transthoracic echocardiography					
LVEF (%)	57.5 ± 6.0	58.9 ± 4.5	57.9 ± 6.3	46.7 ± 8.5	<0.001‡§‖
Normal	66.0	59.2	57.0	4.6	<0.001‡§‖
Regional WMA	28.3	32.4	36.7	95.5	<0.001‡§‖
Diffuse WMA	17.0	7.0	11.4	77.3	<0.001‡§‖
Coronary angiography					
Radiographic angiography	94.3	94.4	100.0	100.0	0.117
Coronary CTA	5.7	5.6	0.0	0.0	0.117
Normal coronary arteries	58.5	59.1	50.6	40.9	0.382
Nonobstructive CAD	41.5	40.9	49.4	59.1	0.382
Abnormal ventriculography#	0	36	40	95	<0.001‡§‖¶
CMR characteristics					
LVEF (%)	65.1 ± 8.1	60.9 ± 7.8	60.6 ± 8.5	53.6 ± 13.4	<0.001*‡§‖¶
Regional WMA	0	22.5	58.2	63.6	<0.001*†‡§¶
Pericardial effusion	5.7	1.4	2.5	9.1	0.199
Myocardial T2w abnormality	0	42.3	62.0	68.0	<0.001*‡¶
Perfusion defect**	0	0	25	0	<0.001†‖¶
HR LGE imaging available	84.9	64.8	78.5	59.1	0.021*‡
Definite myocardial LGE	0	100	100	0	<0.001*§‖¶
Possible myocardial LGE	0	0	0	0	NA
Uncertain LGE pattern	0	0	0	0	NA
Transmural LGE	0	0	27.8	0	<0.001†‖¶
LGE extent (number of segments)	0 (0-0)	2 (1-3)	1 (1-3)	0 (0-0)	<0.001*†§‖¶
Pericardial LGE	3.8	2.8	0	0	0.277

Values are mean ± SD, %, or median (interquartile range). *Statistical significance between negative CMR results and myocarditis. †Statistical significance between myocarditis and myocardial infarction. ‡Statistical significance between negative CMR results and takotsubo cardiomyopathy. §Statistical significance between myocarditis and takotsubo cardiomyopathy. ‖Statistical significance between myocardial infarction and takotsubo cardiomyopathy. ¶Statistical significance between negative CMR results and myocardial infarction. #Data not available in 16 (30%), 21 (30%), 17 (22%), and 1 (5%) patient, respectively. **Data not available in 14 (26%), 28 (39%), 25 (32%), and 7 (32%) patients, respectively.

Abbreviations as in Tables 1 to 3.

TABLE 7 Outcomes During Follow-Up According to Initial MINOCA Diagnosis

	Total Population With Available Follow-Up (n = 116)	Negative CMR Results (n = 21)	Myocarditis (n = 47)	Myocardial Infarction (n = 34)	Takotsubo Cardiomyopathy (n = 12)	Uncertain CMR Results (n = 2)	p Value
Follow-up duration (yrs)	2.9 (1.0–3.7)	2.8 (1.7–3.3)	2.5 (0.9–3.9)	3.0 (1.3–4.8)	3.2 (2.6–3.6)	3.2 (1.7–4.6)	0.28
New hospitalization in cardiology	20 (17)	4 (19)	2 (4)	13 (38)	1 (8)	0 (0)	<0.001*†
Recurrence of acute coronary syndrome	8 (7)	1 (5)	3 (6)	4 (12)	0 (0)	0 (0)	0.22
Diagnosis consistent with initial diagnosis	7/8	0/1	3/3	4/4	NA	NA	NA
Death	5 (4)	0 (0)	2 (4)	3 (9)	0 (0)	0 (0)	0.17
Death of cardiac cause	1 (1)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0.24

Values are median (interquartile range) or n (%). *Statistical significance between negative CMR results and myocarditis. †Statistical significance between myocarditis and myocardial infarction.
CMR = cardiac magnetic resonance; MINOCA = myocardial infarction with nonobstructed coronary arteries; NA = not applicable.

CLINICAL IMPLICATIONS. The management of patients with MINOCA and uncertain diagnosis is a major dilemma in clinical cardiology. In these, myocardial infarction has not been ruled out or ascertained, and therapeutic management remains empirical or based on observational nonrandomized studies (26,27). A variety of methods have been proposed to detect occult causes of infarction, including imaging the coronary wall with intravascular ultrasound (28) or optical coherence tomography (29) or identifying a biological substrate for thrombophilia (30). The present study suggests that increasing the spatial resolution of CMR may also be instrumental in retaining or excluding the diagnosis of myocardial infarction, with major implications for patient management. Given that most cardiac magnetic resonance vendors have free-breathing LGE solutions available, our study supports the systematic integration of the method in patients undergoing CMR in the context of MINOCA, particularly when conventional CMR results are inconclusive. Applying such strategy would lead to a prolongation of the CMR study of about 10 min in about 40% of the patients, which in our opinion is acceptable.

STUDY LIMITATIONS. A main limitation was the absence of follow-up data in part of our population. Unfortunately, standardized follow-up was not practical in patients managed outside our institution. Another limitation was the absence of HR LGE imaging in 25% of the patients. For practical reasons, a prolongation of the CMR study in every patient was not compatible with our clinical work flow. However, HR LGE imaging was systematically performed when conventional CMR methods were inconclusive, which is the population benefiting the most from HR LGE imaging. HR LGE imaging was also performed in a sufficient number of patients with conclusive conventional CMR to conclude that the method is less valuable in this population. Last, because T1 and T2 mapping methods (31) were not locally available when the study was initiated, the incremental diagnostic value of HR LGE imaging in comparison with a CMR protocol including these sequences has not been evaluated.

CONCLUSIONS

In patients with MINOCA, the addition of HR LGE imaging using a free-breathing method improves the detection and assessment of the transmural distribution of myocardial injuries. This translates into changes in final diagnosis in about one-half of the patients with inconclusive findings after conventional CMR methods. In particular, HR LGE imaging can ascertain or rule out the diagnosis of myocardial infarction in a significant number of patients. These results have major implications for the management of patients with MINOCA.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Improving the spatial resolution of LGE imaging leads to a lower rate of noncontributory CMR in patients with MINOCA.

TRANSLATIONAL OUTLOOK: Future research should aim at developing LGE CMR methods with higher spatial resolution and acceptable acquisition times to be implemented as part of standard care for the diagnostic management of patients with MINOCA.

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KEY WORDS cardiac magnetic resonance, late gadolinium enhancement, myocardial infarction with nonobstructed coronary arteries

APPENDIX For the CMR protocol and pulse sequence parameters and supplemental figures and a table, please see the online version of this paper.