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HOW TO USE IMAGING

How to Use Cardiac Magnetic Resonance Imaging in Myocardial Infarction With Nonobstructive Coronary Arteries

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ABSTRACT: The working diagnosis Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA) is being increasingly recognized with the common use of high-sensitivity troponins and coronary angiography, accounting for 5% to 10% of all acute myocardial infarction presentations. Cardiac magnetic resonance (CMR) imaging is pivotal in patients presenting with suspected MINOCA, mainly to delineate those with a nonischemic cause, for example, myocarditis and Takotsubo syndrome, from those with true ischemic myocardial infarction, that is, MINOCA. The optimal timing for CMR imaging in patients with suspected MINOCA has been uncertain and, until recently, not been examined prospectively. Previous retrospective studies have indicated that the diagnostic yield decreases with time from the acute event. The SMINC studies (Stockholm Myocardial Infarction with Normal Coronaries) show that CMR should be performed early in all patients with the working diagnosis of MINOCA, with the possible exception of patients who are clearly identified as having Takotsubo syndrome as determined by echocardiography. In addition to CMR imaging, other investigations of importance in selected patients may be pulmonary artery computed tomography to exclude pulmonary embolism, optical coherence tomography to identify plaque disruption, and acetylcholine provocation to identify coronary artery spasm. Imaging of patients with the working diagnosis MINOCA, which is centered on CMR together with supplemental investigations, results in a clear diagnosis in approximately three-quarters of the patients. This is a good example of personalized medicine, because a correct diagnosis will not only increase the satisfaction of the individual patient but also result in optimizing treatment without harming the patient.

Key Words: magnetic resonance imaging ■ MINOCA ■ myocardial infarction ■ myocarditis ■ Takotsubo cardiomyopathy

The diagnostic criteria of Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA) have been established in key position papers by the European Society of Cardiology and the American Heart Association, which comprise (1) criteria for an acute myocardial infarction; (2) absence of obstructive coronary artery disease, that is, no lesion causing ≥50% stenosis; and (3) no clinically overt cause for the acute presentation.[1,2] The condition is being increasingly recognized with the common use of high-sensitivity troponins and coronary angiography, accounting for 5% to 10% of all acute myocardial infarction presentations.[3] The above position papers emphasize the importance of considering MINOCA as a working diagnosis, where the underlying mechanism responsible for the acute presentation requires further investigation. Moreover, the fourth universal definition of myocardial infarction highlighted the importance of delineating myocardial injury, that is, elevated cardiac troponin, from myocardial infarction, which requires both evidence of myocardial injury and evidence of ischemia to make the diagnosis. Thus, in patients presenting with suspected MINOCA, it is important to delineate those with a nonischemic cause, for example, myocarditis and Takotsubo syndrome, from those with true ischemic myocardial infarction, that is, MINOCA.[4] These seminal position papers,[1,2,4] along with contemporary European Society of Cardiology guidelines for management of acute coronary syndromes,[5]

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have highlighted the use of cardiac magnetic resonance (CMR) imaging in the investigation of patients with suspected MINOCA, primarily to exclude nonischemic causes. Accordingly, several studies have suggested that CMR changes the provisional diagnosis in the majority of MINOCA cases.[6,7] Thus, the main diagnostic challenge is to establish the diagnoses of myocardial infarction, myocarditis, and Takotsubo syndrome by CMR (Figures 1 through 3) in the highest possible proportion of patients with the working diagnosis of MINOCA.

CMR IN MINOCA

Previous Studies

There is now an abundance of publications on CMR imaging in MINOCA. In general, the studies are small, usually 100 to 250 patients, and retrospective.[8–19] The majority of studies have shown high diagnostic yields, sometimes in up to 100% of the patients with suspected MINOCA. The results about the different diagnoses are heavily influenced by the selection of patients. Typically, younger male patients with suspected MINOCA tend to have a high proportion of myocarditis, whereas older female patients with suspected MINOCA tend to have a high proportion of Takotsubo syndrome as their final diagnosis, particularly when cases with ST elevation are included (Table). There are 4 systematic reviews including meta-analyses. First, Tornvall et al[20] included 5 studies comprising 556 MINOCA patients, which showed that 33% of the patients had myocarditis that was associated with young age and high CRP (C-reactive protein). Twenty-one percent had a true myocardial infarction that was associated with male sex, treated hyperlipidemia, high troponin, and low CRP. Second, Hausvater et al[21] included 27 studies with a total of 2866 patients, which showed a prevalence of myocarditis of 34% that was associated with young age, male sex, and angiographically normal coronary arteries. Eighteen percent had a true myocardial infarction without association with the angiographic definition. Third, Balakrishna et al[22] included 18 studies comprising 2697 patients,

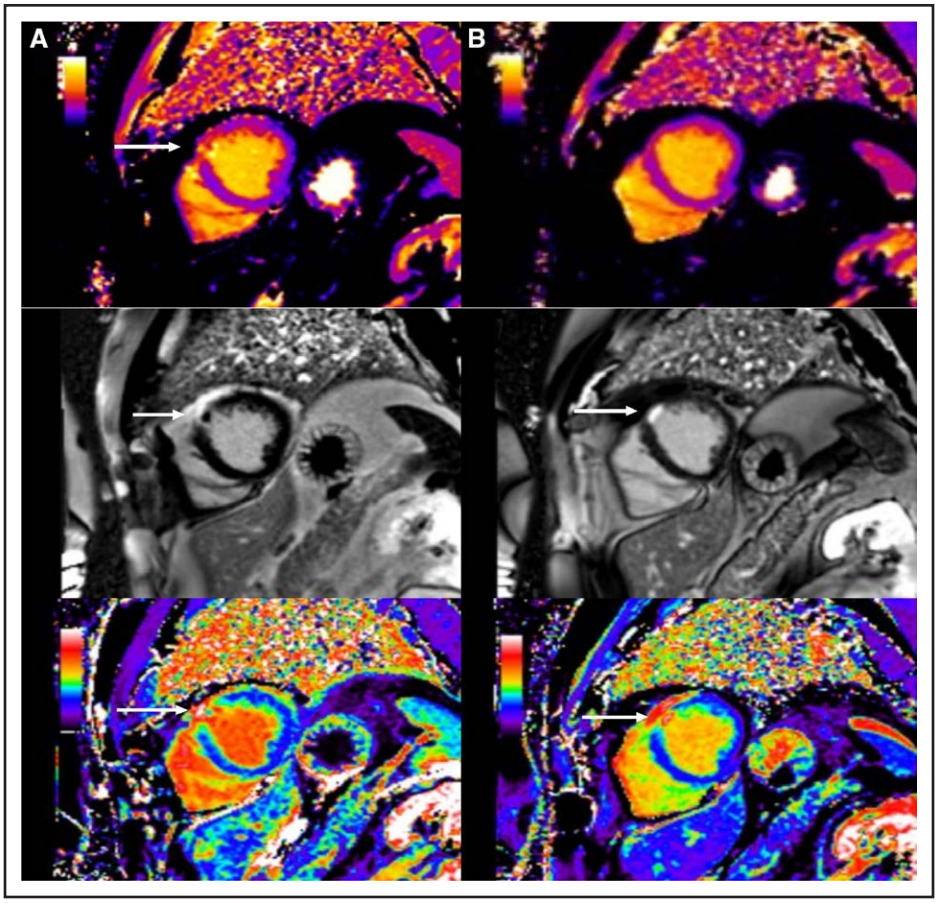

Figure 1. Cardiac magnetic resonance imaging results of myocardial infarction obtained 2 to 4 days and 6 months after hospitalization in a patient with myocardial infarction with nonobstructive coronary arteries.
Myocardial infarction in the anteroseptal wall indicated by the white arrows. Column (**A**) 2 to 4 days: Increased signal in native T1-mapping, phase-sensitive inversion recovery (PSIR), and extracellular volume (ECV). Column (**B**) 6 months: Normal signal in native T1-mapping but remaining scar in PSIR and ECV. Native T1-mapping (first row); PSIR (second row); and ECV (third row).

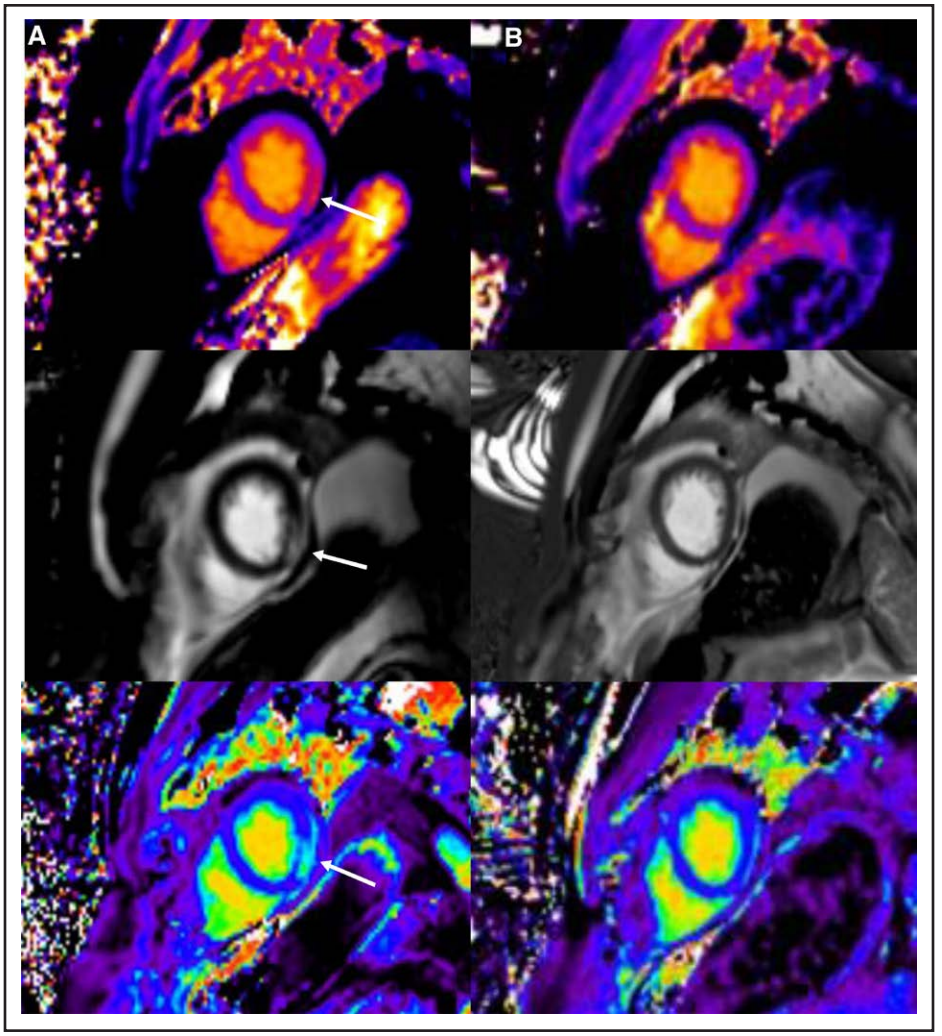

Figure 2. Cardiac magnetic resonance imaging results of myocarditis obtained 2 to 4 days and 6 months after hospitalization in a patient with myocardial infarction with nonobstructive coronary arteries.
Myocarditis in the inferior apical wall indicated by the white arrows. Column (**A**) 2 to 4 days: Increased signal in native T1-mapping, phase-sensitive inversion recovery (PSIR), and extracellular volume (ECV). Column (**B**) 6 months: Normal signal in native T1-mapping and no scar on PSIR and ECV. Native T_1-mapping (first row); PSIR (second row); and ECV (third row).

which showed that 29% had myocarditis and 18% had true myocardial infarction. They also reported that optical coherence tomography improved the likelihood of a diagnosis from 74% to 85%–100%, depending on the study. Fourth, Mileva et al[23] included 26 studies with a total of 3626 patients, which showed that 31% of the patients had myocarditis and 22% had true myocardial infarction. They also reported that the prevalence of Takotsubo syndrome was 10%.

Taken together, these studies showed that ≈20% of the patients had true myocardial infarction and one-third of the patients had myocarditis, whereas the proportion of Takotsubo syndrome was low. The systematic reviews should be interpreted with caution since there is a large heterogeneity between the studies, in particular about the timing of the CMR imaging in relation to the admission of suspected MINOCA. None of the mentioned reviews have focused on the timing of CMR.

Optimal Timing

The optimal timing for CMR imaging in patients with suspected MINOCA has been uncertain and, until recently, not been examined prospectively. The timing of CMR in relation to anatomic testing with invasive coronary angiography or coronary computed tomography angiography also represents a gap in knowledge. Previous studies[8–19] have indicated that the diagnostic yield decreases with time from the acute event (Table). Dastidar et al[6] retrospectively compared early (≤2 weeks) with late (>2 weeks) CMR imaging. They showed that the diagnostic yield of CMR imaging was improved from 51% to 88% when CMR was performed early. The clinical impact, determined by the change in diagnosis and management of the patient, also increased from 51% to 76%.

Prospective studies yield insights about the best timing of CMR imaging in patients with suspected MINOCA.

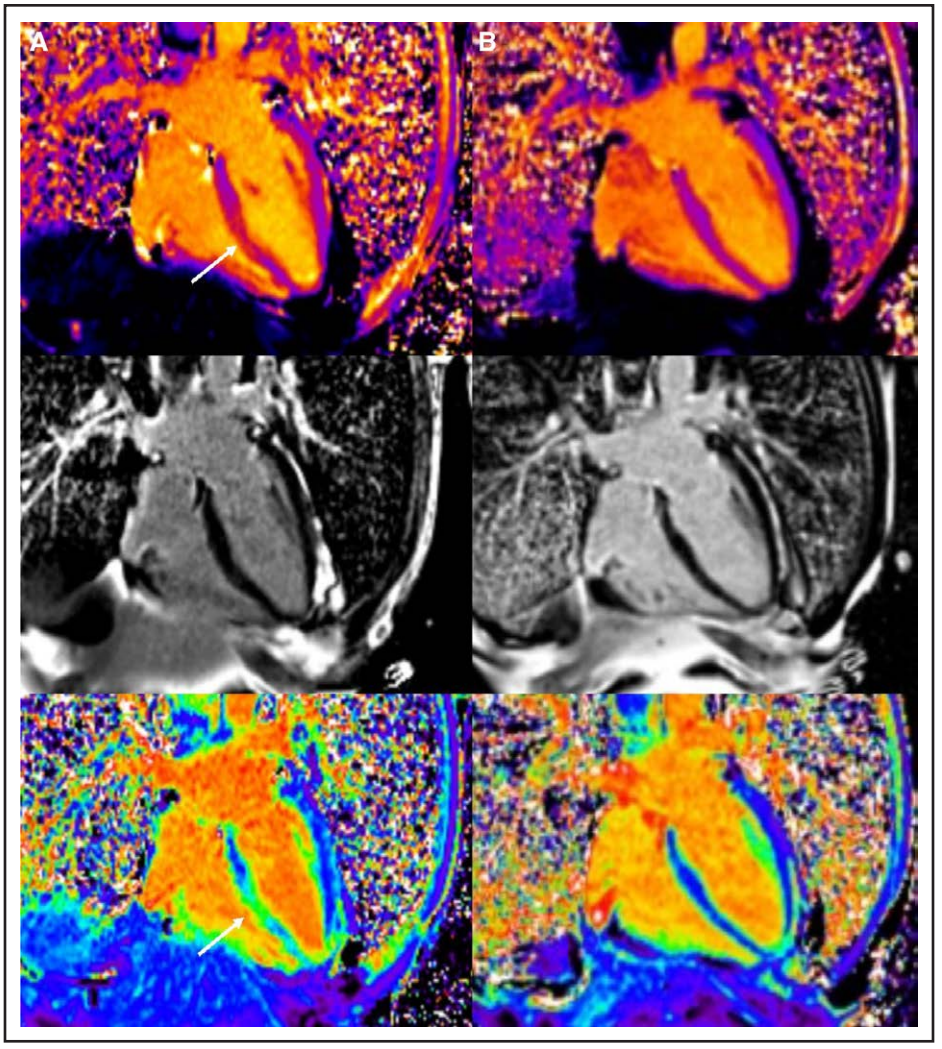

Figure 3. Cardiac magnetic resonance imaging results of Takotsubo syndrome obtained 2 to 4 days and 6 months after hospitalization in a patient with myocardial infarction with nonobstructive coronary arteries.
Takotsubo syndrome in the midventricular part of the septum indicated by the white arrows. Column (**A**) 2 to 4 days: Increased signal in native T1-mapping and extracellular volume (ECV), normal phase-sensitive inversion recovery (PSIR). Column (**B**) 6 months: Normal signal in native T1-mapping and ECV, no scar in PSIR. Native T1-mapping (first row); PSIR (second row); and ECV (third row).

The Women's Heart Attack Research Program included 116 women with MINOCA who underwent CMR and suggested that the likelihood of an abnormal versus normal CMR was more common with an early CMR investigation.[17] The SMINC study (Stockholm Myocardial Infarction with Normal Coronaries) program has been pivotal in demonstrating the importance of early CMR imaging to achieve the highest possible diagnostic yield in patients with suspected MINOCA. In 2013, Collste et al[18] described that two-thirds of 152 prospectively enrolled patients with suspected MINOCA had a normal CMR investigation in the median 12 days after hospitalization in the first SMINC-1 study. It was not possible to determine if the patient had had Takotsubo syndrome with this late CMR investigation, but if clinical suspicion, mainly left ventricular angiography and echocardiography, of Takotsubo was added to the CMR findings, almost 50% of the patients received a diagnosis. One strength of SMINC-1 was the prospective nature of the study. The majority of studies at that time and later[8–19] showed a much higher diagnostic yield, sometimes up to 100% (Table). However, these studies were typically retrospective, for example, because of a referral made after suspicion of heart disease after an echocardiography showed dilated or hypertrophic cardiomyopathy. This inflated the likelihood of finding a diagnosis. Another key reason includes the relatively late timing of the CMR investigation in SMINC-1.

In SMINC-2, CMR imaging was performed 2 to 4 days after index hospitalization because of suspected MINOCA, and the results were compared with those in SMINC-1. The CMR protocol in SMINC-2 was more comprehensive and included T1 and extracellular volume mapping, reflecting advances in imaging since the time of the initial study. The second SMINC (SMINC-2) study was published in *Journal of American College*

Table. Cardiac Magnetic Resonance Imaging Studies of >100 Patients With Myocardial Infarction With Nonobstructive Coronary Arteries With Time From Hospitalization to Investigation

CMR timing	Age, y	Female sex	No.	Diagnosis	Normal	MI	MC	Other	Ref
3 d	54	34%	125	100%	0%	16%	42%	62%	8
3 d	42	66%	250	86%	14%	22%	54%	10%	9
3 d	58	33%	145	99%	1%	15%	33%	51%	10
4 d	50	52%	190	85%	15%	21%	47%	17%	11
4 d	55	49%	215	83%	17%	22%	32%	29%	12
4 d	56	53%	227	79%	21%	24%	27%	28%	13
5 d	44	37%	107	90%	10%	16%	60%	14%	14
6 d	54	48%	130	77%	23%	29%	26%	22%	15
6 d	54	55%	229	85%	15%	28%	38%	19%	16
6 d	59	100%	116	74%	26%	33%	15%	27%	17
12 d	58	64%	152	33%	67%	19%	7%	5%	18
30 d	57	51%	719	74%	26%	26%	26%	22%	19

CMR indicates cardiac magnetic resonance imaging; MC, myocarditis; MI, myocardial infarction (diagnosis required late gadolinium enhancement); Other, cardiomyopathies, Takotsubo syndrome, regional edema and undecided; and Ref, reference.

of Cardiology Cardiovascular Imaging 2021[24] with a prespecified 6-month follow-up in the same journal.[25] Similar inclusion (first myocardial infarction, age 35–70 years, and sinus rhythm) and exclusion (pulmonary embolism, severe chronic obstructive pulmonary disease, known cardiomyopathy, or severe renal impairment) criteria were used. The reasons for the age limits were: 35 years to exclude patients with obvious myocarditis, and 70 years to include the majority of patients with myocardial infarction since only a minority of patients above 70 years of age underwent a coronary angiography at the start of SMINC-1 in 2007.

In SMINC-2, 77% of 148 patients with a working diagnosis of MINOCA received a final diagnosis based on CMR imaging.[24] When comparing the SMINC-1 and SMINC-2 cohorts, the diagnostic yield improved for both myocarditis (7% to 17%) and Takotsubo syndrome (19% to 35%). There were no cases with an uncertain CMR diagnosis, but CMR was normal in 23% of the cases. Interestingly, the diagnostic yield for myocardial infarction was unchanged. The results emphasize the clinical value of performing an early CMR investigation. The results were reinforced by the follow-up CMR of 113 MINOCA patients,[25] which showed that signs of myocardial infarction were unchanged (Figure 1B) and myocarditis had disappeared in 50% of the patients after 6 months (Figure 2B). Furthermore, all patients with Takotsubo syndrome had a normal CMR investigation, supporting their initial diagnosis (Figure 3B).

Central illustration of the main findings of SMINC-2 is shown in Figure 4.

The results of the SMINC-2 study have also shed light on other imaging modalities for suspected MINOCA, in particular Takotsubo syndrome. The results showed that the sensitivity and specificity of left ventricular angiography, made for clinical reasons, were moderate (77% and 72%, respectively) for Takotsubo when using CMR imaging as the gold standard. In contrast, the specificity for echocardiography, made for clinical reasons, was high (95%), whereas the sensitivity was low (57%) in comparison with CMR imaging. One prespecified analysis was echocardiography, made the same day as CMR for research purposes, to investigate the utility of echocardiography as a possible method of selecting patients for CMR. The results showed that only one-third of the patients with a normal echocardiography had a normal CMR investigation 2 to 4 days after hospitalization. The remaining patients had either myocardial infarction or myocarditis, as determined by CMR imaging.[26] Thus, echocardiography is inadequate to determine which patients may have a diagnostic CMR, likely reflecting the far greater resolution of CMR along with the improved ability to characterize tissue properties by CMR as compared with standard echocardiography. In conclusion, the results emphasize the importance of an early CMR investigation in patients with suspected MINOCA without an obvious reason.

CMR Techniques

The diagnostic value of different CMR techniques is uncertain in MINOCA. According to the original Lake Louise criteria for myocarditis, early gadolinium enhancement (EGE) can be used. The increased signal of an interstitial contrast agent could be visualized and semiquantitatively assessed in T1-weighted CMR images before and early after contrast administration using the myocardial signal intensity enhancement relative to skeletal muscle. EGE is still considered useful but not often used in most centers because of the inconsistency of image quality. Data indicate that removing EGE from

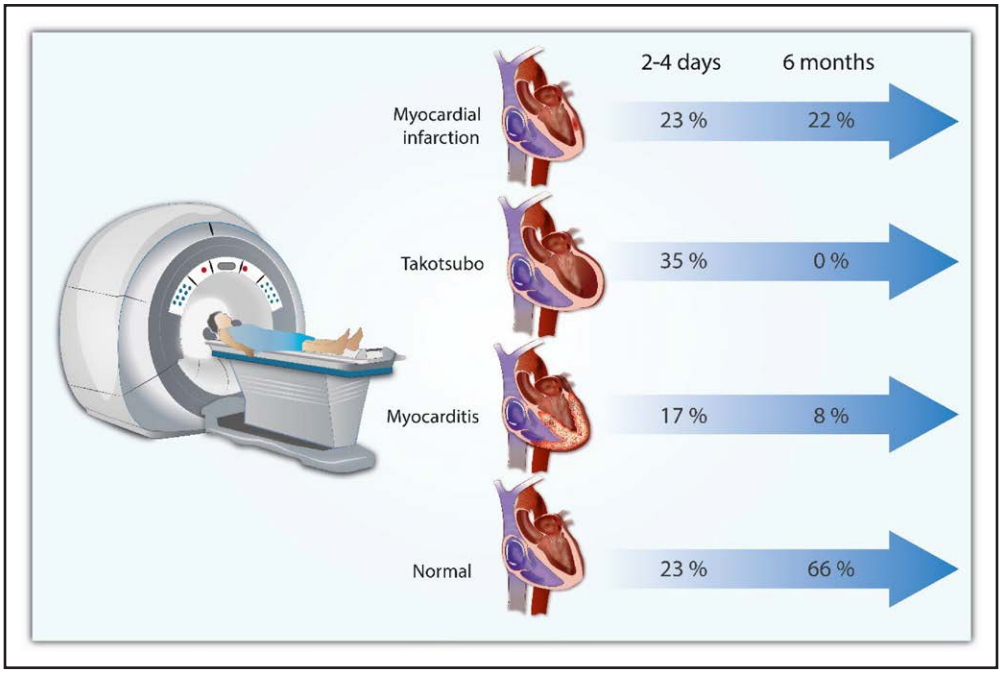

Figure 4. Main findings of the SMINC-2 study (Stockholm Myocardial Infarction with Normal Coronaries).
Cardiac magnetic resonance imaging was performed 2 to 4 days and 6 months after hospitalization. The percentages denote the relative diagnostic yield with respect to the most common diagnoses.

the original Lake Louise criteria does not significantly reduce diagnostic accuracy for myocarditis.[27] Centers experienced in myocardial mapping sequences may thus prefer to omit EGE. There is a lack of evidence for the added value of EGE in the context of patients with MINOCA, and few studies or centers have implemented this sequence. Regarding late gadolinium enhancement, magnitude inversion recovery is highly sensitive to the selected inversion recovery time (TI) with a loss in contrast if TI is shorter than the null time of normal myocardial tissue; therefore, phase-sensitive inversion recovery is preferred for late gadolinium enhancement. The hyperintense signal in T2-weighted short tau inversion recovery imaging has the potential to show edema based on prolonged T2 relaxation times from the accumulation of interstitial water, which has been suggested as an early marker of acute myocardial ischemia.[28] While the clinical implications are promising, T2-weighted short tau inversion recovery has been shown to be prone to image artifacts, such as posterior-wall signal loss due to motion and subendocardial bright rim artifacts due to slow-flowing blood. The parametric T2-mapping can overcome some of the limitations of T2-weighted short tau inversion recovery imaging as it can directly quantify the T2-relaxation time, does not rely on relative signal enhancement, and provides a more reliable alternative to T2-weighted short tau inversion recovery.[29] Multiparametric mapping, including T1, T2, and extracellular volume (ECV), has shown great promise in diagnosing myocarditis and is included in the updated 2018 Lake Louise criteria. The criteria suggest that the use of T1-based markers, for example, T1-mapping or ECV, provides strong evidence for acute myocardial inflammation in patients with a significant clinical pretest probability, whereas T2-based markers, for example, T2-mapping, can be used to identify edema. Recently, there has been an increased interest in simultaneous multiparametric mapping, including but not limited to magnetic resonance multitasking, multiparametric saturation recovery single-shot acquisition, and cardiovascular magnetic resonance fingerprinting. Unfortunately, there are no studies of the value of multiparametric mapping in MINOCA. However, by combining edema sequences (T1 and T2) without late gadolinium enhancement and optical coherence tomography, Reynolds et al[17] showed that it was possible to show an ischemic origin of MINOCA.

Clinical Perspective

Taken together, the results from the SMINC studies show that CMR imaging should be performed early to increase the diagnostic yield in all patients with suspected MINOCA, with the possible exception for patients with suspected MINOCA who are clearly identified as having Takotsubo syndrome as determined by echocardiography. Other exceptions include patients with a high likelihood of type 2 myocardial infarction due to, for example, anemia or high-rate atrial fibrillation,[4] and patients with contraindications for CMR, such as cardiac devices that are noncompatible with CMR. Besides absolute contraindications for CMR imaging, a relatively high number of patients have difficulties

undergoing CMR due to claustrophobia, and it is important to avoid investigating hemodynamically unstable patients in CMR laboratories without relevant cardiological expertise.

In addition to CMR imaging, other investigations of importance in selected patients could be pulmonary artery computed tomography to exclude pulmonary embolism, optical coherence tomography to identify plaque disruption, acetylcholine provocation to identify coronary artery spasm, and positron emission tomography. Please see Figure 5 for a diagnostic algorithm for the investigation of patients with a working diagnosis of MINOCA. Imaging of patients with suspected MINOCA, which is centered on CMR together with supplemental investigations, results in a clear diagnosis in approximately three-fourth of the patients. This is a good example of personalized medicine, because a correct diagnosis will not only increase the satisfaction of

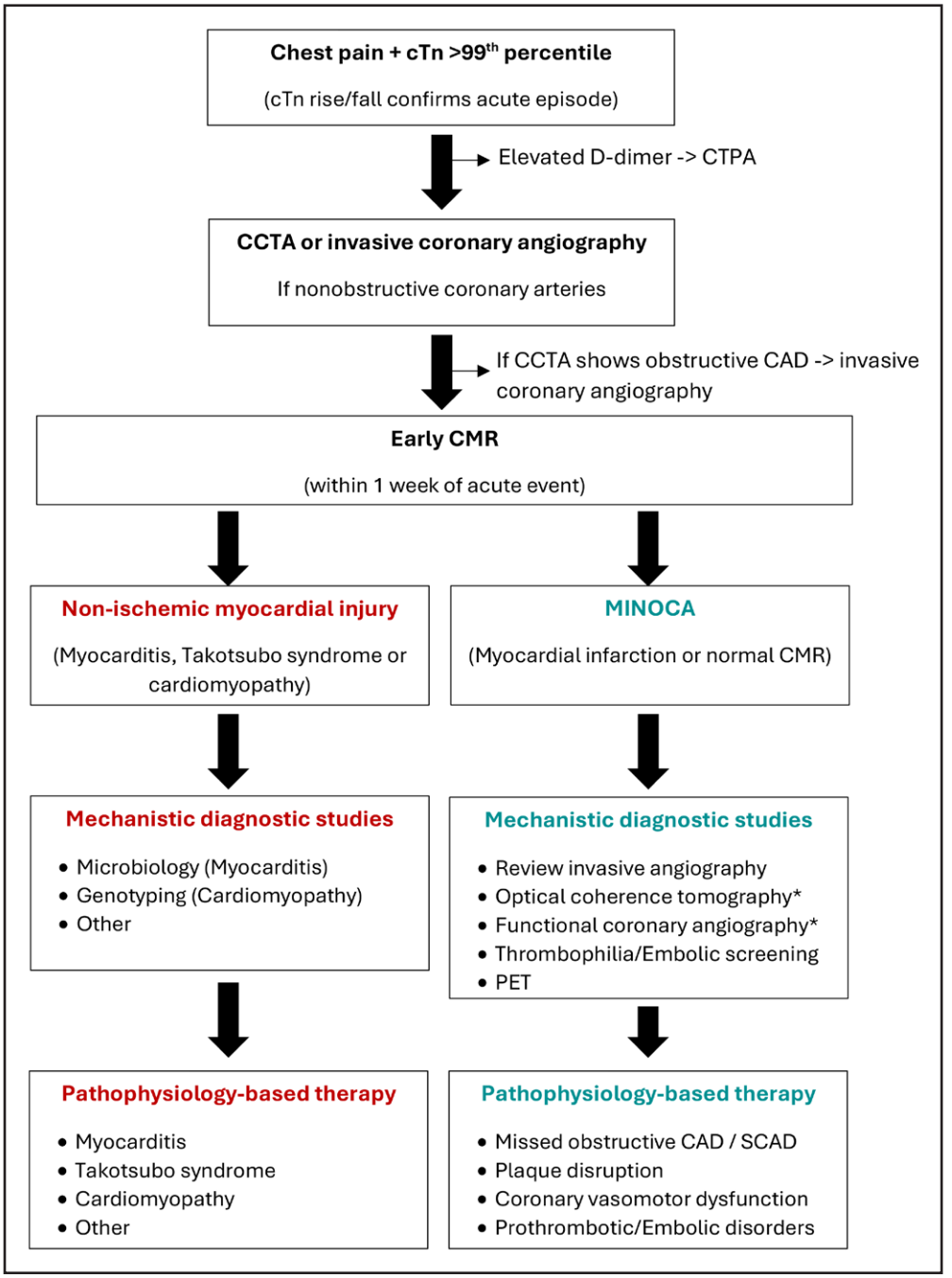

Figure 5. Diagnosis and management of suspected myocardial infarction with nonobstructive coronary arteries (MINOCA).
*Can be performed during index invasive coronary angiography. CAD indicates coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance imaging; CTPA, computed tomography pulmonary angiography; PET, positron emission tomography; and SCAD, spontaneous coronary artery dissection.

the individual patient but also result in optimizing treatment without harming the patient. For example, patients with a CMR-verified true myocardial infarction should be considered for statins and anti-platelet therapy, whereas patients with uncomplicated CMR-verified myocarditis could be treated with NSAIDS to relieve chest pain. Uncertainties remain about the treatment of patients with Takotsubo syndrome, where a recent meta-analysis points against treatment with angiotensin-converting enzyme/A2-inhibition and beta-blockers.[30] Currently, it is unclear if patients with suspected MINOCA with normal investigations, including an early CMR, should have the final diagnosis of MINOCA and be treated as a CMR-verified myocardial infarction. Some of these patients will be shown to have plaque disruption if optical coherence tomography is performed and should thus be treated for myocardial infarction. Further research focused on this group of patients is needed to identify underlying diagnoses, for example, to determine the potential role of microvascular dysfunction. Finally, the results of CMR imaging may contain prognostic information. Mileva et al[23] showed in a meta-analysis, including 770 patients, that a CMR diagnosis of myocardial infarction was associated with major adverse cardiovascular events.

ARTICLE INFORMATION

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