Radiology: Cardiothoracic Imaging

REVIEW

Cardiac MRI Assessment of Nonischemic Myocardial Inflammation: State of the Art Review and Update on Myocarditis Associated with COVID-19 Vaccination

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Myocarditis is a nonischemic inflammatory disease of the myocardium that can be triggered by a multitude of events, including viral infection and toxins. Recently, there has been heightened interest in myocarditis given its association with COVID-19 vaccination. Timely identification of myocarditis can affect patient management and prognosis. Therefore, it is crucial for radiologists and cardiac imagers to understand the role of cardiac imaging to establish a diagnosis and inform treatment decisions. Cardiac MRI is the most important noninvasive imaging modality for evaluation of myocarditis, with typical findings of focal or diffuse myocardial edema and myocardial damage, including presence of late gadolinium enhancement. There are currently limited data available to indicate that the pattern of myocardial injury following COVID-19 vaccination is similar to other causes of myocarditis, although the severity of disease may be relatively mild. A description of the role of imaging and typical imaging features will be reviewed here, with a focus on emerging data in the setting of myocarditis after COVID-19 vaccination.

Myocardial inflammation is an important cause of myocardial injury, which often results from the host immune response, and can be triggered by infection, autoimmune diseases, ischemic injury, or toxins. *Myocarditis* is a more specific term, defined as a nonischemic inflammatory disease of the myocardium. Traditionally, diagnosis has relied on histologic evaluation of the myocardium showing inflammation and myocyte damage (1). Recently, there has been heightened awareness of myocarditis due to reports of myocardial inflammation after COVID-19 illness and vaccination. Cardiac MRI plays an important role in the assessment of suspected myocarditis, as timely identification can affect patient management and prognosis (2). The aim of this review is to provide an overview of the role of cardiac MRI and typical findings in patients with nonischemic myocardial inflammation, with a focus on emerging data in the setting of acute myocarditis after COVID-19 vaccination.

Incidence and Pathophysiology of Myocarditis

The incidence of myocarditis is difficult to establish, as clinical symptoms are nonspecific, including chest pain and shortness of breath, and endomyocardial biopsy is not frequently performed for definitive diagnosis. Approximately one-third of patients presenting with acute coronary syndrome without substantial coronary artery disease are ultimately diagnosed with acute myocarditis (3).

Even across diverse causes (Table 1), myocarditis is ultimately driven by an immune response directed at cardiomyocytes. In acute myocarditis, the initial trigger is either direct myocardial injury or immune dysregulation that induces inflammation by activating an innate or adaptive immune response. Myocardial injury can manifest across a spectrum of clinical severity—from subclinical disease, to myocarditis with preserved cardiac function, to more severe cases that result in reduced systolic or diastolic function, arrhythmia, and rarely hemodynamic collapse and cardiogenic shock. In most patients, the immune response is self-limited and downregulates with clearance of the initial trigger. However, depending on the degree of myocardial injury, patients may have residual myocardial dysfunction and fibrosis. In a minority of patients, the inflammatory response can persist or recur, leading to chronic myocarditis. Most patients recover completely after acute myocarditis, but a small proportion, estimated at less than 5%, will progress to dilated cardiomyopathy due to myocardial remodeling (Fig 1) (4).

The most common trigger for myocarditis in developed countries is viral infection (5,6). Although traditional serologic studies, viral cultures, and molecular techniques can be used to identify viral pathogens in the setting of myocarditis, these techniques lack both sensitivity and specificity (7). Myocardial injury is also associated with COVID-19 illness, with elevated troponin levels in more than 60% of hospitalized patients (8). Although SARS-CoV-2 can infect cardiomyocytes by binding to the angiotensin-converting enzyme 2, indirect myocardial inflammation due to immune dysregulation may be a more prominent mechanism of myocardial injury (8).

Abbreviations

ECV = extracellular volume, LGE = late gadolinium enhancement, LLC = Lake Louise criteria, LV = left ventricular, VAERS = U.S. Vaccine Adverse Event Reporting System

Summary

Radiologists and other cardiac imagers should understand the role of cardiac imaging and typical features in the setting of myocarditis, including after COVID-19 vaccination, given that timely identification can affect patient treatment and prognosis.

Essentials

- Cardiac MRI is the most important noninvasive cardiac imaging modality for the evaluation of myocarditis with typical imaging findings including myocardial edema and late gadolinium enhancement.
- Myocarditis can be triggered by a multitude of events, although recent attention has focused on the association with COVID-19 vaccination, particularly in younger males.
- Limited data to date indicate that the pattern of myocardial injury following COVID-19 vaccination is similar to other causes of myocarditis; the disease severity may be relatively mild, although outcome data are lacking, and further study is needed.

Keywords

MRI, Heart, Inflammation

Noninfectious causes of myocardial inflammation include autoimmune and immune-mediated disorders such as vasculitides, connective tissue disorders such as systemic lupus erythematosus, and granulomatous diseases such as giant cell myocarditis. Several drugs and medications are associated with myocarditis, including amphetamines and immune checkpoint inhibitors. Myocarditis is an uncommon adverse event after immunization (9). However, there is emerging evidence that COVID-19 vaccination is associated with myocarditis in a minority of patients.

Diagnosis

Establishing a diagnosis of acute myocarditis is important, as timely recognition can impact patient management and outcomes (2). Myocarditis is an important cause of sudden cardiac death in young adults, accounting for up to 12% of sudden cardiac death cases, according to postmortem analysis (10). Due to increased risk of sudden cardiac death, particularly when performing exercise, avoidance of competitive sports is typically recommended for at least 3 months in patients with acute myocarditis (11).

Endomyocardial biopsy is still considered the reference standard for definitive diagnosis of myocarditis; however, it is not frequently performed due to the invasive nature of the procedure and associated risks, as well as low sensitivity compared with cardiac explant at autopsy (12). Endomyocardial biopsy is usually only indicated if there is clinical evidence that the results will have a meaningful effect on therapeutic decisions (13). When endomyocardial biopsy is performed, the Dallas criteria are commonly used, which require histologic evidence of inflammatory infiltrates within the myocardium associated with myocyte damage and/or necrosis of nonischemic origin for definitive diagnosis (Fig 2) (7). Newer proposed criteria rely on immunohistochemical techniques, which may be more sensitive (14).

In clinical practice, diagnostic criteria for suspected myocarditis that are based on expert consensus are more commonly employed. Acute myocarditis is considered clinically suspected if at least one clinical criterion and at least one diagnostic criterion are met (15). Clinical criteria include acute chest pain, new onset dyspnea, palpitations, unexplained arrhythmia symptoms, syncope, aborted sudden cardiac death, and unexplained cardiogenic shock. Diagnostic criteria include electrocardiographic, Holter monitor, or stress test abnormalities; elevated troponin levels; functional and structural abnormalities at cardiac imaging; and typical tissue characterization features of edema and/or late gadolinium enhancement (LGE) at cardiac MRI. Cardiac MRI can be used to meet either of the latter two criteria, highlighting the important role of imaging for diagnosis in acute myocarditis (15). Imaging findings can also be useful in identifying or excluding other potential diagnoses that may have a similar clinical presentation, including acute coronary syndrome or stress-induced cardiomyopathy. In some circumstances, imaging findings may suggest a specific potential cause for myocardial injury, although there is substantial overlap in imaging findings between different causes of myocarditis.

Imaging Myocardial Inflammation

The American Heart Association recommends testing for patients with signs consistent with myocarditis, using one or more cardiac imaging techniques, such as echocardiography or cardiac MRI (16).

Echocardiography

Echocardiography is often the first imaging modality used in patients with suspected myocarditis, as it is widely available and allows for relatively rapid assessment of cardiac size and function. Typical findings, including increased myocardial wall thickness and echogenicity, impaired global systolic function and strain, regional wall motion abnormalities, and ventricular dilatation, are relatively nonspecific (17). However, echocardiography provides important prognostic information, as increased left ventricular (LV) size and impaired function are predictors of poor outcomes (18).

CT Imaging

Coronary CT angiography is a noninvasive imaging modality that may be useful in excluding obstructive coronary artery disease in patients presenting with acute chest pain and elevated troponin levels, due to its high negative predictive value. Late iodine enhancement may be useful in evaluating myocardial damage, particularly in patients with a contraindication to MRI, although there are limited data specifically in acute myocarditis (19).

PET Imaging

Fluorodeoxyglucose PET is well established in the evaluation of active myocardial inflammation in the setting of cardiac sarcoidosis. Limited data available demonstrate that fluoro-

Table 1: Causes of Myocardial Inflammation and Typical MRI Findings

Cause	Specific Cause or Mechanism	Key MRI Finding
Infection	Infectious agents can induce cardiac injury by directly infecting cardiomyocytes or through cellular or humoral immune activation Viral: Enteroviruses, coronaviruses, adenoviruses, parvovirus B19, herpesviridae 6, CMV, EBV, HIV, influenza; SARS-CoV-2 can infect cardiomyocytes by binding to the ACE2 receptor, although immune dysregulation is likely a more prominent mechanism of myocardial injury Bacterial: *Borrelia burgdorferi* (Lyme disease), *Treponema pallidum*, group A *Streptococcus* (likely postinfectious) Protozoal: *Trypanosoma cruzi* (Chagas disease), *Toxoplasma gondii* Parasitic: *Echinococcus granulosus*, *Trichinella spiralis*	Viral myocarditis: Linear subepicardial or midwall LGE, commonly involving the basal inferolateral wall, basal anterior septum, mid inferolateral wall, and basal to mid inferior wall, with corresponding T2 hyperintensity or high T2 Chagas disease: LGE present in up to 70% of patients, most commonly at the left ventricular apex, apical inferior and lateral wall, and basal to mid inferolateral wall; LGE is usually midwall or subepicardial and less commonly subendocardial or transmural with apical aneurysms Bacterial and parasitic myocarditis: Limited data on MRI findings with no specific pattern COVID-19: Findings may be similar to non-COVID viral myocarditis, although some studies have indicated a higher prevalence of diffuse myocardial edema, with global elevation of T1 and T2 mapping values
Postvaccination	mRNA COVID-19 vaccines: Proposed mechanisms include immune activation and dysregulation and molecular mimicry between viral spike protein and an unknown cardiac protein	mRNA COVID-19 vaccination: There are currently limited MRI data, mostly from case series to date; MRI findings appear to be typical for viral myocarditis, although the severity and extent of MRI abnormalities reported have been relatively mild; axillary lymphadenopathy ipsilateral to the vaccination site may be present and may be a useful clue, particularly if a history of recent vaccine administration is not provided
Systemic disease	Several systemic diseases are associated with myocardial inflammation Vasculitides: EGPA, Kawasaki disease Connective tissue disorders: Systemic sclerosis, SLE, rheumatoid arthritis, dermatomyositis Granulomatous disease: Sarcoidosis	EGPA: MRI findings include patchy midwall and subepicardial LGE with corresponding T2 hyperintensity and subendocardial apical LGE with or without apical thrombus; concomitant pulmonary opacities might be present SLE: Patchy or linear midwall and subepicardial LGE in one-third of patients; elevated T1 and T2 value decrease following anti-inflammatory treatment; higher prevalence of pericardial and pleural effusion and thickening than in other causes of myocarditis Sarcoidosis: Patchy and nodular LGE with associated high T2, most common at the basal septum and basal inferolateral segment; associated findings include mediastinal and hilar lymphadenopathy and pulmonary opacities
Drug related	Hypersensitivity reactions: Penicillin, cephalosporins, benzodiazepines, tricyclic antidepressants Toxic reactions: Anthracyclines, amphetamines, cyclophosphamide Immune activation or dysregulation: ICI-related myocarditis	ICI-related myocarditis: Diffusely elevated T1 and T2 values in 78% and 43% of patients, respectively; in one study, only 48% of patients met both T1 and T2 modified Lake Louise criteria; LGE present in 48% of patients, most commonly subepicardial or midmyocardial, and predominating in the basal and mid inferior and inferolateral segments
Other	Hypereosinophilic syndrome, cocaine, postradiation injury, thyrotoxicosis, giant cell myocarditis	Hypereosinophilic syndrome: Similar MRI findings to EGPA, with higher prevalence of subendocardial LGE Giant cell myocarditis: MRI appearance is similar to cardiac sarcoidosis, although LGE tends to be more extensive and right ventricular involvement more common

Note.—ACE2 = angiotensin-converting enzyme 2, CMV = cytomegalovirus, EBV = Epstein-Barr virus, EGPA = eosinophilic granulomatosis with polyangiitis, ICI = immune checkpoint inhibitor, LGE = late gadolinium enhancement, SLE = systemic lupus erythematosus.

deoxyglucose PET can also identify inflammation in the setting of acute myocarditis (20). PET is typically performed in conjunction with CT for anatomic localization, although more recently combined PET/MRI scanners have become available, which could provide complementary information from both modalities in patients with myocarditis (21).

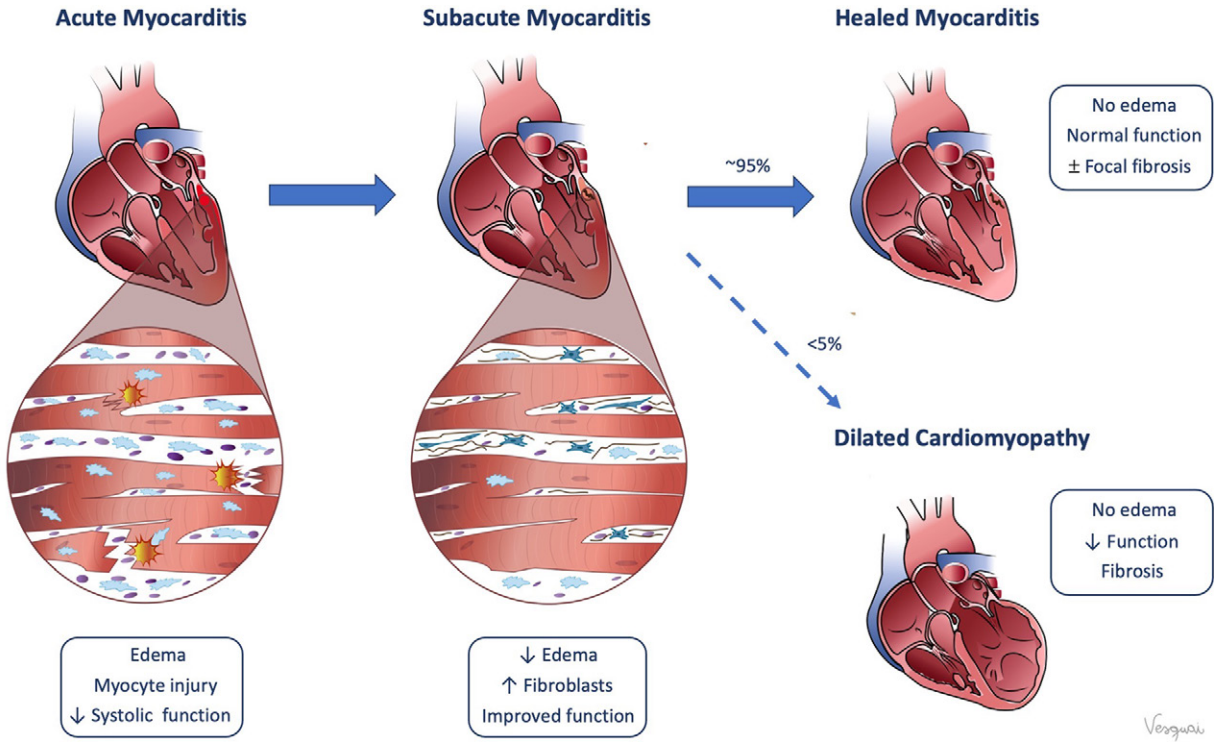

Figure 1: Pathophysiology of myocarditis. (Reprinted, with permission, from Valentina Sanchez Tijmes).

Cardiac MRI

Cardiac MRI is the most important noninvasive cardiac imaging modality for the diagnosis, follow-up, and risk stratification of patients with nonischemic myocardial inflammation, with unparalleled ability to characterize myocardial tissue. According to the 2021 American Heart Association/American College of Cardiology/American Society of Echocardiography/American College of Chest Physicians/Society for Academic Emergency Medicine/Society of Cardiovascular Computed Tomography/Society for Cardiovascular Magnetic Resonance Guideline for the Evaluation and Diagnosis of Chest Pain, cardiac MRI is useful in distinguishing myocarditis from other causes of acute chest pain in patients with myocardial injury who have nonobstructive coronary arteries at anatomic testing. Cardiac MRI is also useful in patients with suspected myocarditis or myopericarditis if there is diagnostic uncertainty or to determine the presence and extent of myocardial or pericardial inflammation and fibrosis (22).

Updated Lake Louise Criteria

MRI findings of myocardial inflammation are commonly assessed using expert consensus guidelines, the Lake Louise criteria (LLC), initially published in 2009. These criteria were broadly used in clinical practice, although evaluation was limited due to subjectivity in qualitative assessment and moderate diagnostic sensitivity (23). The LLC were revised in 2018 to incorporate parametric mapping, which allows for quantitative assessment of regional and global myocardial T1 and T2 relaxation times and extracellular volume (ECV) (24). In comparison to the original LLC, the revised criteria have significantly higher sensitivity (88% vs 73%) while maintaining very high specificity (96%) (25). According to the revised criteria, cardiac MRI provides strong evidence of acute myocardial inflammation in patients with high clinical pretest probability if at least one criterion in each of the following two categories is positive: a T2-based marker of myocardial edema and a T1-based marker of myocardial damage (Fig 3). The presence of only one marker may still support the diagnosis of myocardial inflammation in the appropriate clinical context, although with lower specificity. Importantly, these criteria were intended to be applied in patients with clinically suspected myocardial inflammation and not applied broadly as a screening test for myocardial injury in asymptomatic patients.

T2-based Criteria for Myocardial Edema

Tissue edema is a hallmark of inflammation that is often focal in the setting of myocarditis, although diffuse edema can also be identified (26). T2-based criteria for myocardial edema include regional high T2 signal intensity, global T2 signal intensity ratio equal to or greater than 2.0 on T2-weighted images, or regional or global increase of myocardial T2 relaxation time.

Assessment of myocardial edema at cardiac MRI was previously reliant on T2-weighted imaging, which has high diagnostic accuracy for focal edema, although image quality can be degraded by artifact and signal inhomogeneity, limiting reproducibility (27). T2 mapping allows for direct quantification of T2 relaxation times and is particularly useful for ruling out active inflammation given its very high sensitivity (89%) (28). High T2 signal is specific for increased tissue water and therefore can discriminate between active and healed myocarditis (29).

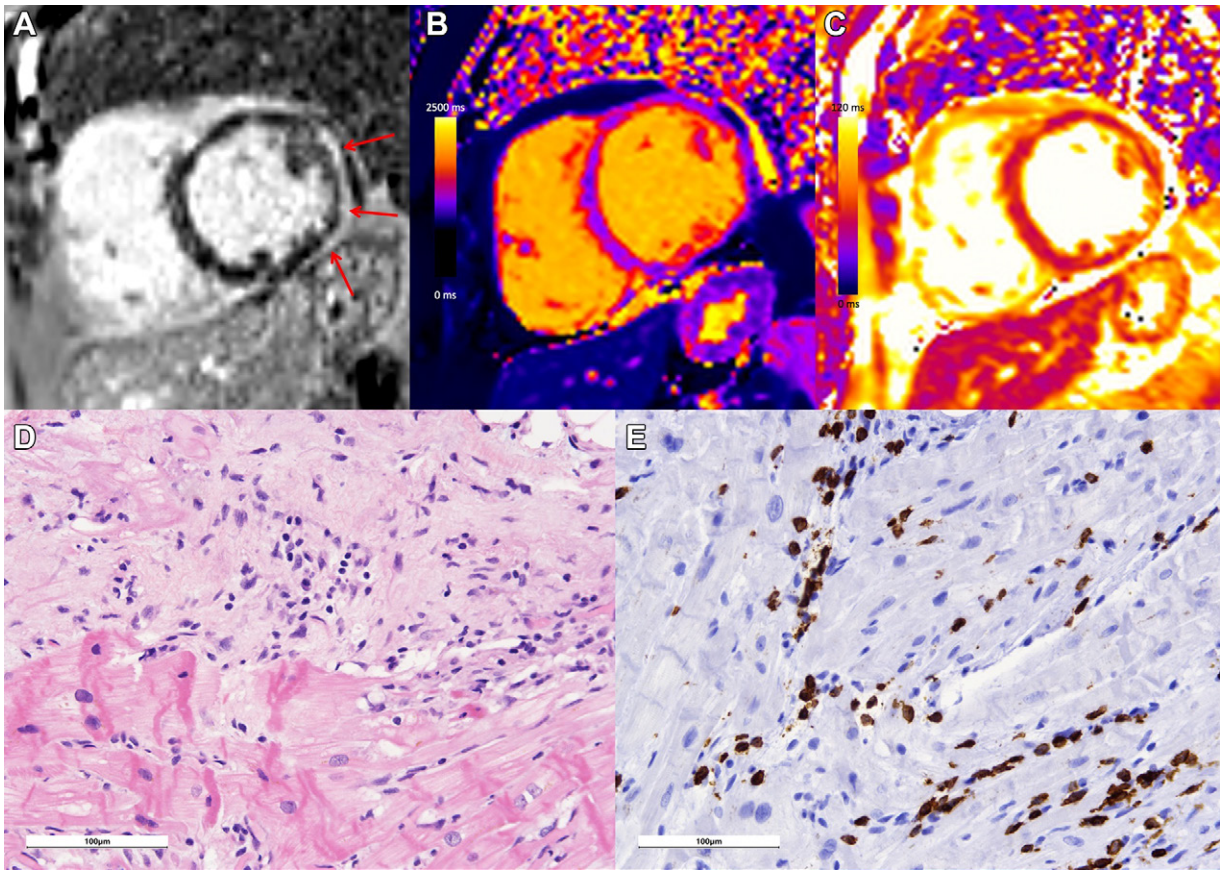

Figure 2: Case example in a 68-year-old woman with lymphocytic myocarditis related to immune checkpoint inhibitor therapy. Cardiac MRI performed at 1.5 T demonstrates extensive subepicardial late gadolinium enhancement at **(A)** the basal to mid anterior, anterior lateral, inferior lateral, and inferior wall (red arrows) with **(B)** corresponding high regional native T1 (1280 msec) and **(C)** high regional T2 (69 msec) on short-axis images, in keeping with myocardial edema and damage. **(D)** Histologic images from endomyocardial biopsy demonstrate inflammation, including an active (dense inflammation) and healing (looser mixed inflammation, expanded matrix) component, with myocyte damage evident as myocytolytic change, vacuolization, and atrophy on hematoxylin-eosin stain. **(E)** At CD3 immunohistochemistry, a substantial portion of the inflammatory population was CD3 positive, consistent with a T-cell–mediated (lymphocytic) active myocarditis. Both histologic images were acquired with a Leica DM2500 microscope with a 20× objective and an OMAX A35180U3 camera. Images were acquired with ToupView software; no further adjustments were made. Scale bars (100 μm) are as shown.

T1-based Criteria for Myocardial Injury

If myocardial inflammation is severe enough, it can result in myocardial injury and necrosis, ultimately leading to fibrosis. T1 criteria for myocardial injury include LGE in a nonischemic pattern or regional or global increase of myocardial native T1 or ECV values.

LGE imaging remains one of the most important MRI techniques in the setting of suspected myocarditis, given that the presence of myocardial damage is a characteristic feature of myocarditis. Gadolinium-based contrast agents are retained within injured and necrotic tissue, resulting in hyperintensity at T1-weighted inversion-recovery imaging. The pattern of LGE in patients with myocarditis is most commonly subepicardial or midwall and often in a linear configuration. On the other hand, the pattern of LGE in the setting of ischemic myocardial injury is subendocardial to transmural and corresponds to a coronary artery territory. The most common location for LGE in viral myocarditis is the basal inferolateral wall. Other segments that are frequently involved include the basal anterior septum, mid inferolateral wall, and basal to mid inferior wall. Transmural enhancement and more diffuse LGE have been described, particularly in severe cases of fulminant and giant cell myocarditis.

LGE is present both in the setting of acute inflammation (with myocyte necrosis and hyperemia) and in the setting of fibrosis (due to expansion of the extracellular space) and therefore cannot reliably differentiate between acute and healed myocarditis (6,24). Over time, the extent of LGE usually decreases as inflammation resolves and scar contracts. T1 and ECV are elevated in the setting of interstitial and replacement myocardial fibrosis. Native T1 is a composite measurement reflecting signal from both the intracellular (mainly myocytes) and extracellular (mainly interstitial) myocardial compartments, while ECV is an estimate of the proportion of the extracellular space only. These parametric mapping techniques may have incremental diagnostic and prognostic value beyond LGE, particularly in the setting of diffuse inflammation, given the ability for direct quantification of myocardial tissue changes.

T1 and ECV are also elevated in the setting of myocardial edema, although unlike elevated T2, these changes are not specific for acute inflammation (29). Given the complementary information provided by T1 and T2 mapping, it is useful to interpret these values together. For example, in a patient with suspected myocarditis, corresponding elevated T2, T1, and ECV values in-

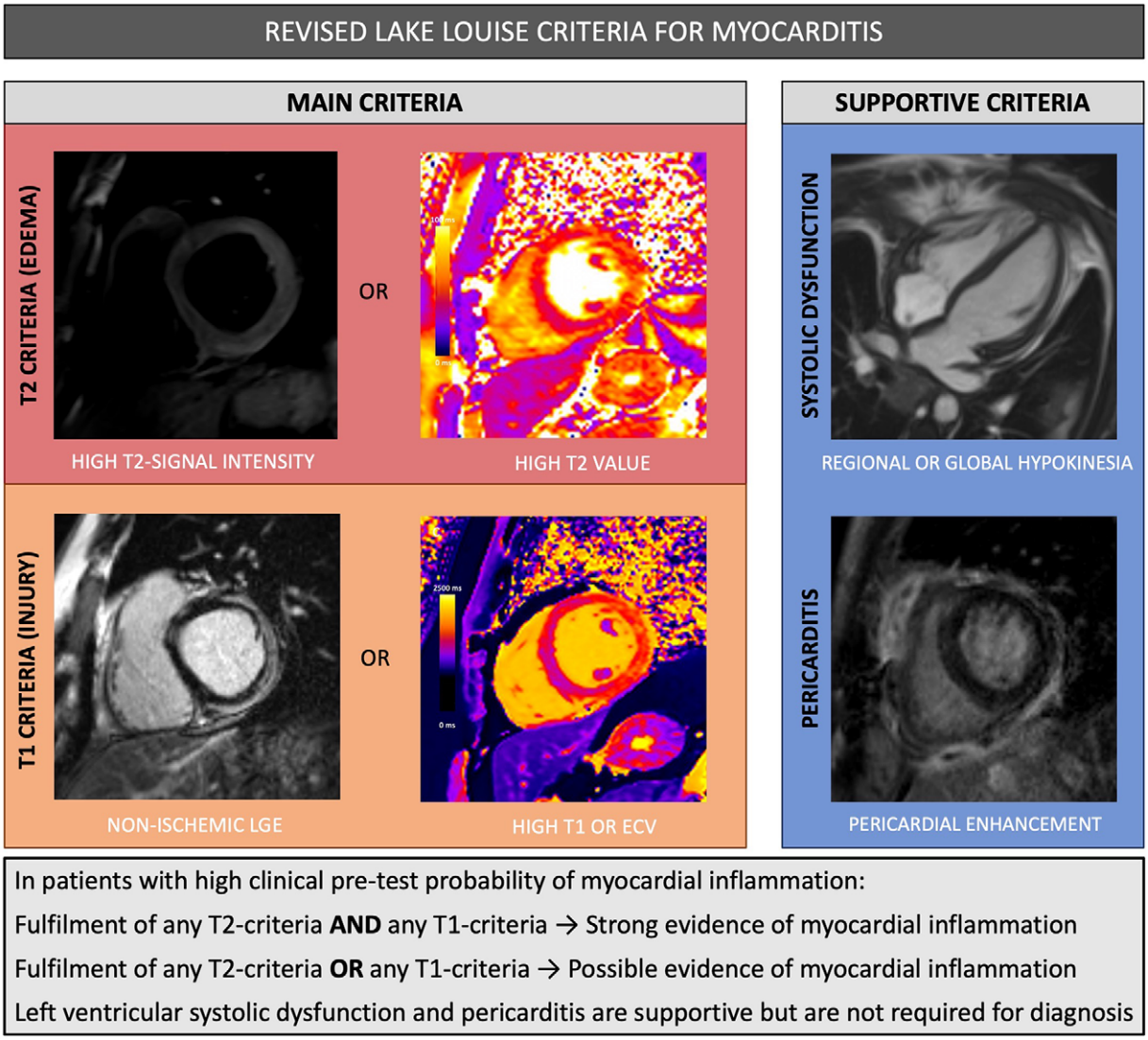

Figure 3: Summary of revised Lake Louise criteria for myocarditis. ECV =extracellular volume, LGE = late gadolinium enhancement.

dicate a high likelihood of myocardial edema, while elevated T1 and ECV in the setting of normal T2 suggest the presence of fibrosis or infiltration without acute inflammation (Fig 4).

LV Dysfunction

In more severe cases of myocarditis, regional wall motion abnormalities and systolic LV dysfunction can be identified at MRI. Systolic LV dysfunction (either regional or global) is a supportive criterion for myocarditis but is not required to make the diagnosis according to the revised LLC. After an acute episode of myocarditis, global systolic function often improves rapidly and, in most cases, returns to normal. Systolic dysfunction is typically more severe in fulminant myocarditis, and despite frequent improvement in the acute phase, LV function remains lower on average compared with nonfulminant cases at long-term follow-up (30). Myocardial strain quantification may increase the sensitivity for subtle wall motion abnormalities but has not been routinely implemented in clinical practice to date (24).

Pericardial Inflammation

Findings of pericardial inflammation are also considered to be supportive for the diagnosis of myocarditis, including pericardial enhancement, high T1 or T2 mapping values, or the presence of a pericardial effusion. When present, concomitant pericarditis is most commonly observed involving the pericardium adjacent to areas of inflamed myocardium, although it can also be diffuse.

Adverse Risk Markers at MRI

LGE is a strong, independent predictor of cardiac and all-cause mortality in patients with myocarditis (31). The risk of major adverse cardiovascular events increases by approximately 79% for every 10% increase in quantitative LGE extent (32). Of note, the presence of LGE with concomitant T2 hyperintensity is associated with better prognosis compared with isolated LGE without T2 hyperintensity. This is most likely due to the fact that LGE without associated edema typically reflects fibrosis, which is irreversible, while LGE in the context of T2 hyper-

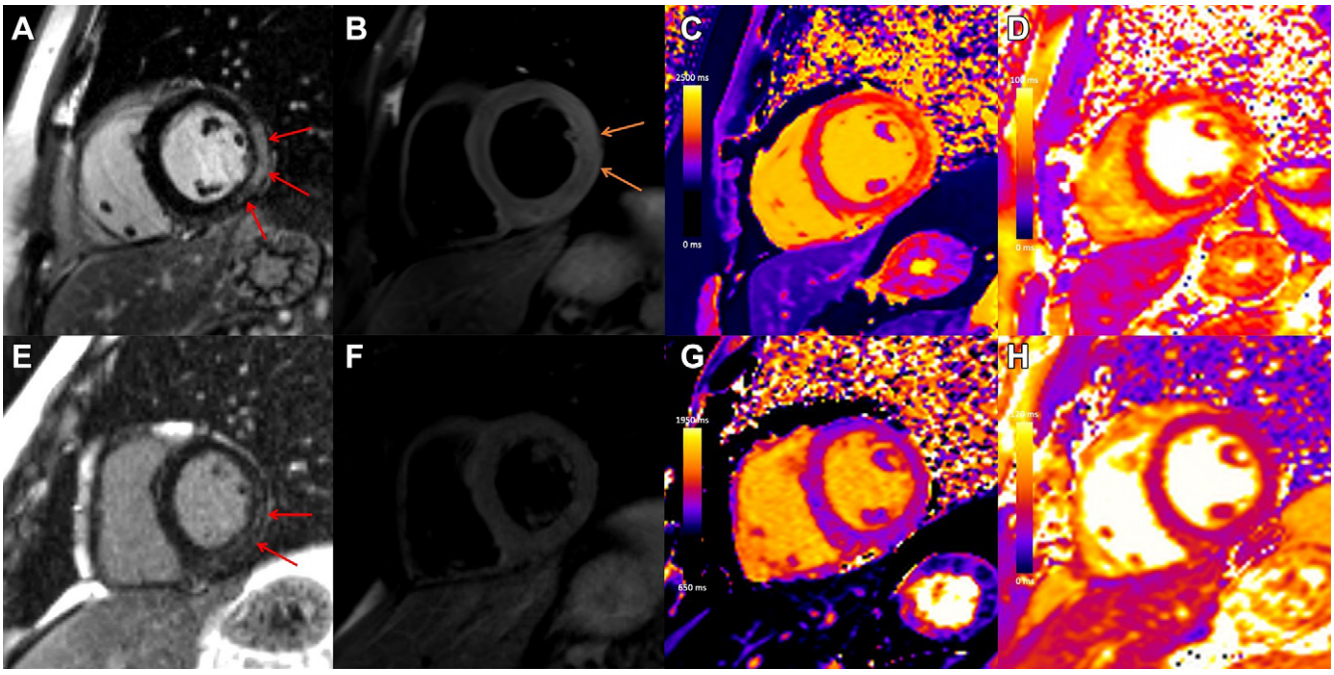

Figure 4: Case example in a 31-year-old man with viral myocarditis. Initial cardiac MRI performed at 3 T within 1 week of symptom onset demonstrates **(A)** subepicardial to nearly transmural late gadolinium enhancement (LGE) at the basal to mid anterior lateral, inferior lateral, and inferior wall (red arrows) with **(B)** corresponding high T2 signal, in keeping with edema (orange arrows), **(C)** high regional native T1 (1480 msec), and **(D)** high regional native T2 (56 msec) on short-axis images. Images from follow-up cardiac MRI performed at 1.5 T 5 months later demonstrate contraction of subepicardial LGE at the basal to mid inferior lateral and inferior wall (**E**, red arrows) with **(G)** corresponding high regional native T1 suggestive of fibrosis (1305 msec) and **(F)** resolution of edema with no corresponding high T2 signal and **(H)** normalization of T2 mapping values (46 msec).

intensity confers the possibility of at least partial recovery as edema improves over time (33). Other important adverse prognostic MRI markers include global systolic dysfunction (LV ejection fraction < 40%) and higher T1 and ECV (32,34). In patients with acute myocarditis with evidence of myocardial edema and/or LV dysfunction, follow-up cardiac MRI may be considered 3 to 6 months after the baseline study to assess for functional recovery and the possibility of residual scarring.

Cardiac MRI Protocol and Postprocessing

In the setting of suspected myocardial inflammation, the MRI protocol should include short- and long-axis cine sequences for assessment of ventricular volumes and function, T2-based imaging (black blood T2-weighted imaging and/or T2 parametric maps), and T1-based imaging (LGE and/or pre– and post–contrast-enhancement T1 mapping) (Table 2).

One important consideration with respect to the evaluation of parametric maps is that values vary substantially on the basis of technical and patient-specific factors, including field strength. T2 values are higher at 1.5 T compared with 3 T, while T1 values are substantially higher at 3 T compared with 1.5 T. Therefore, mapping values should be compared with local reference ranges (35). Maps should be assessed visually as well as quantitatively, including global assessment of diffuse tissue changes along with focal evaluation in myocardial segments that are visually abnormal or demonstrate regional wall motion abnormalities.

For highest diagnostic performance, MRI should ideally be performed in the acute phase. Cardiac MRI markers of myocardial inflammation typically demonstrate rapid and continuous improvement during the first few weeks after the onset of symptoms (36). The sensitivity for detection of myocardial edema in particular is much lower if patients are imaged weeks after the initial clinical presentation. Establishing a diagnosis of nonacute myocarditis is particularly challenging, as findings are often nonspecific.

Cardiac MRI in Specific Causes of Myocarditis

Cardiac MRI findings demonstrate substantial overlap between different causes of myocarditis, and therefore, it is imperative that clinical features are taken into consideration. Clinical and cardiac MRI findings in specific causes of nonischemic myocardial inflammation are summarized in Table 1. Given the recent focus on the role of cardiac imaging in patients with COVID-19 and in patients with suspected myocarditis after COVID-19 vaccination, specific cardiac MRI findings in these settings are highlighted below.

COVID-19

Several cardiac MRI studies have evaluated myocardial damage in patients who recovered from COVID-19, although estimates of myocardial abnormalities have ranged widely, likely reflecting differences in patient populations, including baseline cardiac risk factors and the severity of COVID-19 illness, as well as the timing of imaging after the initial infection. A recent study found that T1 and T2 values were more commonly diffusely elevated in patients recently recovered from COVID-19 compared with patients with non–COVID-19 myocarditis (37). However, other

Table 2: Suggested Cardiac MRI Protocol for Acute Myocarditis

Sequence	Target	Acquisition	Strength	Limitation	Key Analysis and Reporting Point
Core Protocol					
Cine SSFP	Global and regional systolic function	Short-axis stack base to apex Long-axis (two-, three-, and four-chamber) images	Accurate quantification of cardiac volumes, function, and mass Low LVEF strong predictor of adverse outcomes	Artifacts may degrade images and impact the accuracy of quantified values	Biventricular size, ejection fraction, and mass Presence or absence of regional wall motion abnormalities Optional feature tracking strain analysis
LGE	Necrosis and fibrosis	Short-axis stack base to apex Long-axis (two-, three-, and four-chamber) images	Identifies myocardial and pericardial inflammation and fibrosis May be useful in differentiating myocarditis from other diagnoses Strong predictor of adverse outcomes	Cannot reliably differentiate acute from chronic myocarditis Requires administration of contrast agent	Presence or absence, pattern, distribution, and intensity of myocardial LGE Presence or absence and distribution of pericardial enhancement Optional quantification of myocardial LGE extent
T2-weighted Imaging	Edema	Short-axis stack base to apex Optional long-axis images	Visual evaluation of focal edema	Susceptible to artifact and signal inhomogeneity Challenging to identify global edema	Presence or absence, pattern, and distribution of focal myocardial edema on the basis of visual evaluation Presence of global edema on the basis of increased T2 signal intensity ratio greater than or equal to 2 Presence or absence and distribution of pericardial edema
Native T1 mapping*	Edema and fibrosis	Short-axis sections (base, mid, and apex)	Quantification of myocardial tissue changes (regional and diffuse), including both intracellular and extracellular processes Included in the revised LLC T1 criteria for myocardial damage	Sequences may not be available at all centers Local scanner-specific reference values are needed for interpretation Does not differentiate edema from fibrosis	Presence or absence of elevated native T1 values (regional and global) Values should be interpreted in the context of local scanner– and field strength–specific reference ranges
T2 mapping*	Edema	Short-axis sections (base, mid, and apex)	Quantification of myocardial edema (regional and diffuse) Specific for edema Included in the revised LLC T2 criteria for myocardial edema	Sequences may not be available at all centers Local scanner-specific reference values are needed for interpretation Does not detect fibrosis	Presence or absence of elevated native T2 values (regional and global) Values should be interpreted in the context of local scanner– and field strength–specific reference ranges
Optional sequence					
EGE	Hyperemia and capillary leak	Short-axis stack base to apex	Assessment of hyperemia Included in the original LLC	Requires administration of contrast agent Not included in the revised LLC	Presence of regional or global EGE on the basis of EGE ratio greater than or equal to 4

Table 2 (*continues*)

studies have reported more focal MRI abnormalities typical of non-COVID myocarditis in patients who have recovered from COVID-19, including subepicardial LGE (Fig 5) (38). Data regarding MRI findings in COVID-19–related myocardial injury continue to evolve, with multiple large studies currently underway.

Table 2 (*continued*): Suggested Cardiac MRI Protocol for Acute Myocarditis

Sequence	Target	Acquisition	Strength	Limitation	Key Analysis and Reporting Point
First pass perfusion	Hyperemia and capillary leak	Short-axis sections (base, mid, and apex)	Assessment of hyperemia Can be used to exclude substantial coronary artery disease with pharmacologic stress	Requires administration of contrast agent Limited interobserver agreement Not included in the revised LLC	Presence or absence and distribution of perfusion defects Optional quantification of myocardial blood flow
ECV	Extracellular edema and fibrosis	Short-axis sections (base, mid, and apex)	Quantification of the extracellular space Included in the revised LLC T1 criteria for myocardial damage	Requires contemporary hematocrit levels for calculation Requires both pre– and post–contrast-enhanced T1 mapping Requires administration of contrast Sequences may not be available at all centers	Presence or absence of elevated ECV values (regional and global)

Note.—ECV = extracellular volume, EGE = early gadolinium enhancement, LGE = late gadolinium enhancement, LLC = Lake Louise criteria, LVEF = left ventricular ejection fraction, SSFP = steady-state free precession.
*Native T1 and T2 mapping should be included in the core protocol when available, particularly if there is a contraindication to administration of contrast agent that would preclude LGE imaging (T1 mapping) or if T2-weighted imaging is unavailable or degraded by artifact (T2 mapping).

Myocarditis after COVID-19 Vaccination

Myocarditis has been reported in a minority of people following administration of mRNA-based COVID-19 vaccines, including mRNA-1273 (Moderna) and BNT162b2 mRNA (Pfizer-BioNTech), with symptom onset typically within a few days of vaccination (median, 2–3 days). Myocarditis is three to five times more frequent after the second dose compared with the first, although patients with prior history of COVID-19 are at higher risk after the first dose. The U.S. Vaccine Adverse Event Reporting System (VAERS) received 1903 reports of myopericarditis among people who received at least one dose of a COVID-19 vaccine as of August 18, 2021 (9), in the context of nearly 360 million total doses administrated. As of June 2021, there were approximately 40.6 cases of myocarditis reported per million second doses administrated to males aged 12–29 years and 2.4 cases reported per million second doses in men aged 30 years or older (39); for females, reported rates were 4.2 and 1.0 per million second doses for the same categories, respectively. Importantly, VAERS relies on passive reporting, and the data cannot be used to determine whether a vaccine is causally related to an adverse event. Data from the largest integrated health care organization in Israel indicate that vaccination with BNT162b2 mRNA vaccine is associated with an excess risk of myocarditis (risk ratio 3.2 and risk difference 2.7 events per 100 000 persons when compared with age- and risk-matched controls). However, the risk of myocarditis following SARS-CoV-2 infection was much higher (risk ratio 18.3 and risk difference 11.0 events per 100 000 persons) (40).

Given the relatively short time frame with which COVID-19 vaccines have been administered, data regarding the prevalence and pattern of abnormalities at cardiac MRI following vaccination are still emerging. There are only a few published case series describing cardiac MRI findings after COVID-19 vaccination to date, summarized in Table 3. The largest MRI case series of vaccine-associated myocarditis includes 15 patients (range, four to 15 patients). Of note, almost all patients who underwent MRI in the context of myocarditis following COVID-19 vaccination included in case series to date have been hospitalized. It is possible that these patients reflect the more severe end of the spectrum of vaccine-associated myocardial changes due to reporting bias. Typical cardiac MRI findings reported to date in patients with myocarditis following COVID-19 vaccination are similar to findings in nonvaccine myocarditis, including subepicardial LGE with a predilection for the basal inferolateral wall along with corresponding myocardial edema (Fig 6) (41–51). Other findings include pericardial enhancement and axillary lymphadenopathy ipsilateral to the vaccine administration site (52). When reported, impaired LV ejection fraction (<50%–55%) was identified in 14%–25% of patients.

Differentiating vaccine-associated myocarditis from other causes of myocardial injury at cardiac MRI may be a challenge, as the pattern of findings is similar, and there are no longitudinal imaging studies to suggest how long abnormalities persist. However, accurate diagnosis is important, as this could impact patient treatment; current recommendations indicate that individuals who develop myocarditis or pericarditis after a dose of an mRNA vaccine defer receiving a subsequent dose until additional data are available (53). Clinical history, including the timing of symptom onset in relation to vaccine administration, is highly relevant. In patients with signs or symptoms suggestive of myocarditis following vaccination, cardiac MRI should ideally be performed as soon as possible after the onset of symptoms to maximize the likelihood of detecting myocardial edema, which would suggest an acute

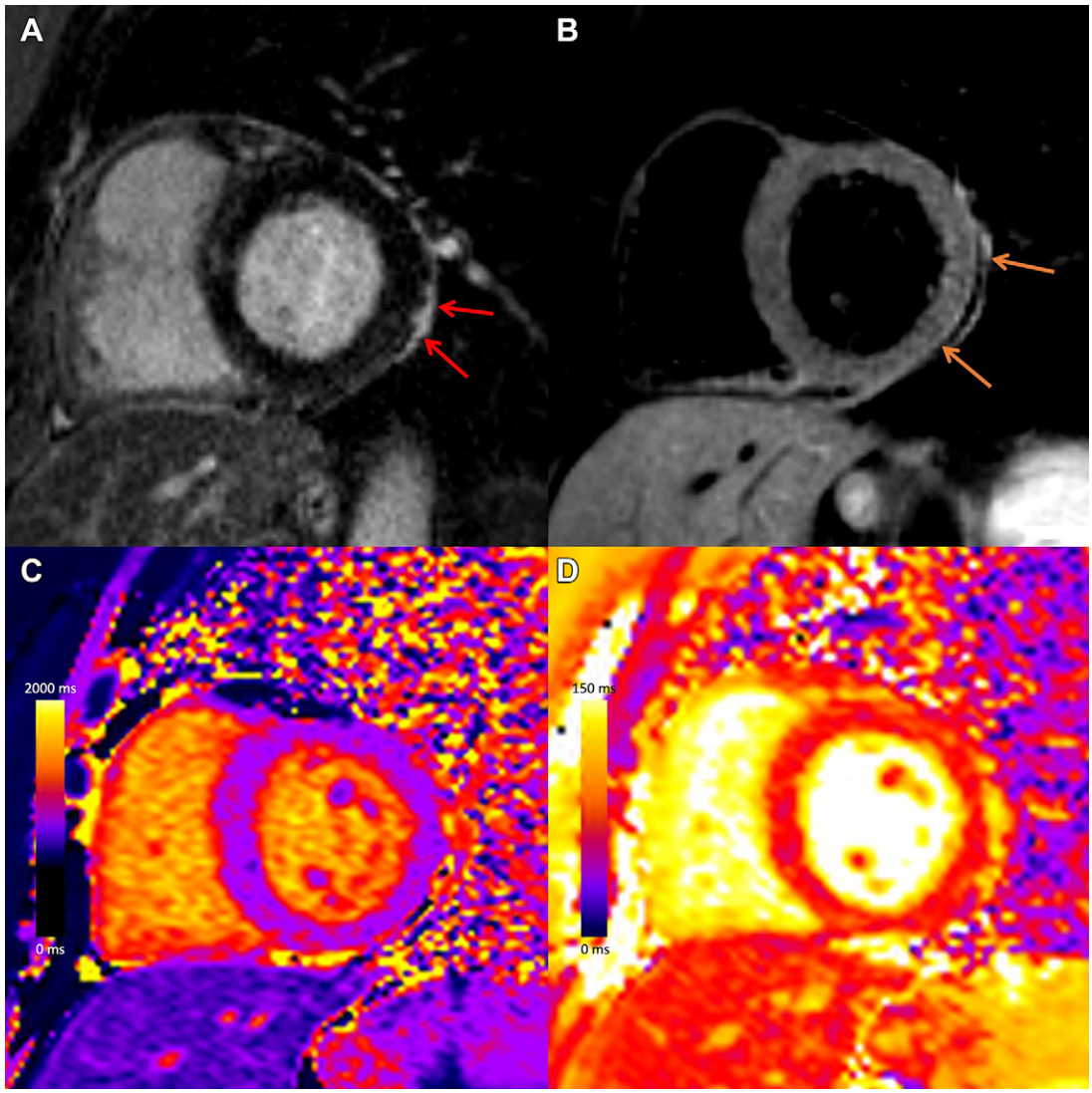

Figure 5: Myocardial injury and pericarditis following COVID-19. Case example in a 57-year-old woman with COVID-19 who presented with chest pain after having elevated troponin levels. Cardiac MRI performed at 1.5 T 4 weeks after polymerase chain reaction–confirmed diagnosis of SARS-CoV-2 infection demonstrates subepicardial late gadolinium enhancement at the **(A)** basal inferior lateral wall with adjacent pericardial enhancement (red arrows), with **(B)** corresponding high T2 signal (orange arrows), and **(C)** high regional native T1 (1236 msec) and **(D)** high regional native T2 (67 msec) on short-axis images, in keeping with myopericarditis.

process (36). If MRI is performed several weeks to months after symptom onset and no T2 abnormality is identified, it is difficult to attribute myocardial tissue changes to a specific cause. This may be a particular challenge in symptomatic patients who have received an mRNA vaccine and have a prior history of COVID-19. Importantly, there are no data to suggest a role for routine imaging or screening of asymptomatic individuals after COVID-19 vaccination in the absence of signs or symptoms suggestive of myocarditis.

In most reported cases of myocarditis following COVID-19 vaccination, the clinical course has been favorable, with rapid resolution of symptoms and corresponding decreases in troponin levels over short-term follow-up, suggesting that patients might have a good long-term prognosis. Given that the risk of myocardial injury and other severe outcomes after COVID-19 is higher, current data are supportive of continued COVID-19 immunization on the basis of the balance of risks and benefits (54). Larger studies with longer-term follow-up are required to evaluate long-term outcomes, to directly compare imaging findings after COVID-19 vaccination to other causes of myocarditis, to assess longitudinal MRI changes after clinical recovery, and to determine the risk associated with subsequent vaccine administration in patients with a prior history of myocarditis.

Conclusion

Cardiac MRI is an important imaging modality in patients with suspected myocardial inflammation and myocarditis, allowing for noninvasive assessment of myocardial edema and injury, and identification of potentially treatable underlying causes of inflammation to guide management and improve patient outcomes. Cardiac MRI may be particularly useful in patients presenting with signs and symptoms suggestive of myocarditis after COVID-19 vaccine administration, although further study is needed.

Table 3: Cardiac MRI Findings after COVID-19 Vaccination

Reference	No. of Patients*	Age† (y)	Vaccine			Presentation after Second Dose	Days between Vaccination and Symptom Onset†	Timing of Cardiac MRI	Other Imaging and Clinical Finding	Cardiac MRI Finding
			Pfizer/ BioNTech	Moderna	J&J					
Patel et al (41)	5 (5)	22 (19–37)	4 (80)	1 (20)	0 (0)	4 (80)	2 (1–3)	1–7 days after symptom onset	All admitted to hospital with elevated troponin levels and chest pain at presentation, all tested negative for COVID-19 at presentation, normal ECG findings in 80% (4/5)	LGE in 100% (5/5), subepicardial (5/5) and midwall (1/5); corresponding edema in three of five (60%) Most common segment involved was the basal inferolateral wall (3/5)
Shaw et al (42)	4 (2)	21 (16–31)	3 (75)	1 (25)	0 (0)	2 (50)	4 (2–5)	N/R	All presented with chest pain and elevated troponin levels; prior history of COVID-19 in 50% (2/4), and both presented with myocarditis after the first vaccine dose	LGE in 100% (4/4), subepicardial (4/4) and midwall (1/4) Corresponding high T2, T1, and ECV in 100% (4/4) Mildly impaired LVEF (54%) in 25% (1/4) Pericardial enhancement in 0% Most common segment involved was the basal inferolateral wall (4/4)
Rosner et al (43)	7 (7)	24 (19–30)	5 (72)	1 (14)	1 (14)	5 (71)	3 (2–7)	3–37 days after vaccination	All admitted to hospital with elevated troponin levels and chest pain at presentation; six of seven tested for COVID-19 at presentation and all negative; one (14%) prior history COVID-19; normal ECG findings in 29% (2/7); clinical symptoms resolved rapidly (with hospital discharge within 4 days)	LGE in 100% (7/7), subepicardial (7/7) and midwall (4/7); distribution not specified Corresponding myocardial edema in 43% (3/7), two with no edema had MRI more than 7 days after presentation and one had artifact on T2 images Impaired LVEF (<50%) in 14% (1/7) and regional wall motion abnormality with hypokinesis in 14% (1/7) Pericardial enhancement in 29% (2/7)
Larson et al (44)	8 (8)	29 (21–56)	5 (63)	3 (37)	0 (0)	7 (88)	3 (2–4)	N/R	All admitted to hospital with elevated troponin levels and chest pain at presentation; all tested negative for COVID-19 at presentation; one (13%) had prior history of COVID-19 (only patient who presented after the first vaccine dose); ECG not reported at baseline; clinical symptoms resolved in 100%	LGE in 100% (8/8); pattern and distribution not specified Myocardial edema in 75% (6/8) Pericardial effusion in 38% (3/8) Impaired LVEF (<50%) in 25% (2/8) Regional wall motion abnormality in 63% (5/8) and generalized hypokinesis in 38% (3/8)

Table 3 (*continues*)

Table 3 (*continued*): Cardiac MRI Findings after COVID-19 Vaccination

Reference	No. of Patients*	Age† (y)	Vaccine			Presentation after Second Dose	Days between Vaccination and Symptom Onset†	Timing of Cardiac MRI	Other Imaging and Clinical Finding	Cardiac MRI Finding
			Pfizer/ BioNTech	Moderna	J&J					
Marshall et al (45)	7 (7)	17 (14–19)	7 (100)	0 (0)	0 (0)	7 (100)	2 (2–4)	1–6 days after symptom onset	All admitted to hospital with elevated troponin levels and chest pain at presentation; 86% (6/7) tested for COVID-19 and all negative; normal ECG findings in 71% (5/7); clinical symptoms resolved rapidly (with hospital discharge within 6 days)	LGE in 100% (7/7), most frequently subepicardial; one patient had diffuse LGE at the left ventricular lateral wall Myocardial edema in 86% (6/7) Most common segments involved were the basal and mid inferolateral wall, basal anterolateral wall, and apical lateral wall Axillary lymphadenopathy in one patient
Kim et al (46)	4 (3)	30 (23–70)	2 (50)	2 (50)	0 (0)	4 (100)	2.5 (1–5)	3–5 days after vaccination	All admitted to hospital with elevated troponin levels and chest pain at presentation; all tested negative for COVID-19 at presentation; ECG not reported; clinical symptoms resolved (with hospital discharge between 2–4 days)	LGE in 100% (4/4), subepicardial (3/4) and patchy or diffuse (1/4); distribution not specified in all Corresponding high T1 in 100% (4/4), but remote T1 was normal in all (4/4) Corresponding myocardial edema in 75% (3/4) Pericardial effusion in 50% (2/4) Pericardial enhancement in 0% Impaired LVEF (<50%) in 25% (1/4)
Abu Mouch et al (47)	6 (6)	23 (16–45)	6 (100)	0 (0)	0 (0)	5 (83)	3 (1–16)	N/R	All admitted to hospital with elevated troponin levels and chest pain at presentation; all tested negative for COVID-19 at presentation; normal ECG findings in 67% (4/6); two of six mildly impaired LVEF (50%–55%); clinical symptoms resolved (with hospital discharge between 4–8 days)	LGE in 100% (6/6), subepicardial (4/6), midwall (2/6), and diffuse (1/6) Corresponding myocardial edema in 100% (6/6) Most common segments involved were basal to mid inferolateral wall, basal to mid anterolateral wall basal anteroseptum, and apex Pericarditis in 17% (1/6)

Table 3 (*continues*)

Table 3 (*continued*): Cardiac MRI Findings after COVID-19 Vaccination

Reference	No. of Patients*	Age† (y)	Vaccine			Presentation after Second Dose	Days between Vaccination and Symptom Onset†	Timing of Cardiac MRI	Other Imaging and Clinical Finding	Cardiac MRI Finding
			Pfizer/ BioNTech	Moderna	J&J					
Starekova et al (48)	5 (4)	21 (17–38)	3 (60)	2 (40)	0 (0)	5 (100)	3 (2–3)	3–5 days after vaccination	All admitted to hospital with elevated troponin levels and chest pain at presentation; all tested negative for COVID-19 at presentation, and none had a prior history of COVID-19; ECG findings not reported; no follow-up data reported	LGE in 100% (5/5), most commonly subepicardial; distribution not specified Corresponding myocardial edema at T2-weighted imaging in 100% (5/5) Pericardial enhancement in 100% (5/5) Axillary lymphadenopathy ipsilateral to the site of vaccination in 80% (4/5)
Montgomery et al (49)	23‡ (23)	25 (20–51)	7 (30)	16 (70)	0 (0)	20 (87)	2.5 (1–5)	N/R	Previously healthy military service members, all presented with chest pain and had elevated troponin levels; hospitalization status not reported; all three presenting after the first vaccine dose had a prior history of COVID-19; normal ECG findings in 83%; LVEF impaired in 17% (4/23); cardiac symptoms resolved within 1 week of onset in 16 of 23	Only eight patients underwent cardiac MRI with limited data reported Subepicardial LGE and/or edema in 100% (8/8)
Dionne et al (50)	15 (14)	15 (12–18)	15 (100)	0 (0)	0 (0)	14 (93)	3 (1–6)	1 to 7 days after symptom onset	All admitted to hospital with elevated troponin levels and chest pain at presentation; ECG demonstrated decreased LVEF in 20% (3/15) and abnormal global longitudinal or circumferential strain in 33% (5/15) All patients discharged from hospital within 5 days; at follow-up (1 to 13 days after discharge), troponin levels remained mildly elevated in 20% (3/15)	MRI consistent with myocarditis in 87% (13/15) LGE present in 80% (12/15); most common segments involved were the basal to mid anterolateral and inferolateral wall Corresponding myocardial edema on T2-weighted imaging in 13% (2/15) High ECV (>30%) in 25% (3/15), and high global native T1 (>1100 msec at 1.5 T) in 13% (2/15) Low LVEF (<55%) in 25% (3/15)

Table 3 (*continues*)

Table 3 (*continued*): Cardiac MRI Findings after COVID-19 Vaccination

Reference	No. of Patients*	Age† (y)	Vaccine			Presentation after Second Dose	Days between Vaccination and Symptom Onset†	Timing of Cardiac MRI	Other Imaging and Clinical Finding	Cardiac MRI Finding
			Pfizer/BioNTech	Moderna	J&J					
Chelada et al (51)	5 (5)	17 (16–19)	4 (80)	1 (20)	0 (0)	5 (100)	4 (3–4)	5–8 days after vaccination	All admitted to hospital with elevated troponin levels and chest pain at presentation; normal ECG findings in 80% (4/5); LVEF impaired in 20% (1/5); during hospital admission, one of five had nonsustained ventricular tachycardia; all patients discharged from hospital within 9 days	LGE in 100% (5/5), subepicardial (4/5) and mid to subepicardial (5/5); most common segments were inferior, inferolateral, and anterolateral Myocardial edema at T2-weighted imaging in 100% (5/5) Low LVEF in 20% (1/5)

Note.—Except where otherwise noted, values are numbers with percentages in parentheses. The three COVID-19 vaccines included Moderna mRNA-1273, Pfizer/BioNTech BNT162b2, and Janssen/Johnson & Johnson Ad26.COV2.S. ECG = electrocardiography, ECV = extracellular volume, LGE = late gadolinium enhancement, LVEF = left ventricular ejection fraction, N/R = not reported.

*Values in parentheses are number of male patients.

†Values are averages with ranges in parentheses.

‡Only eight of the 23 patients underwent cardiac MRI.

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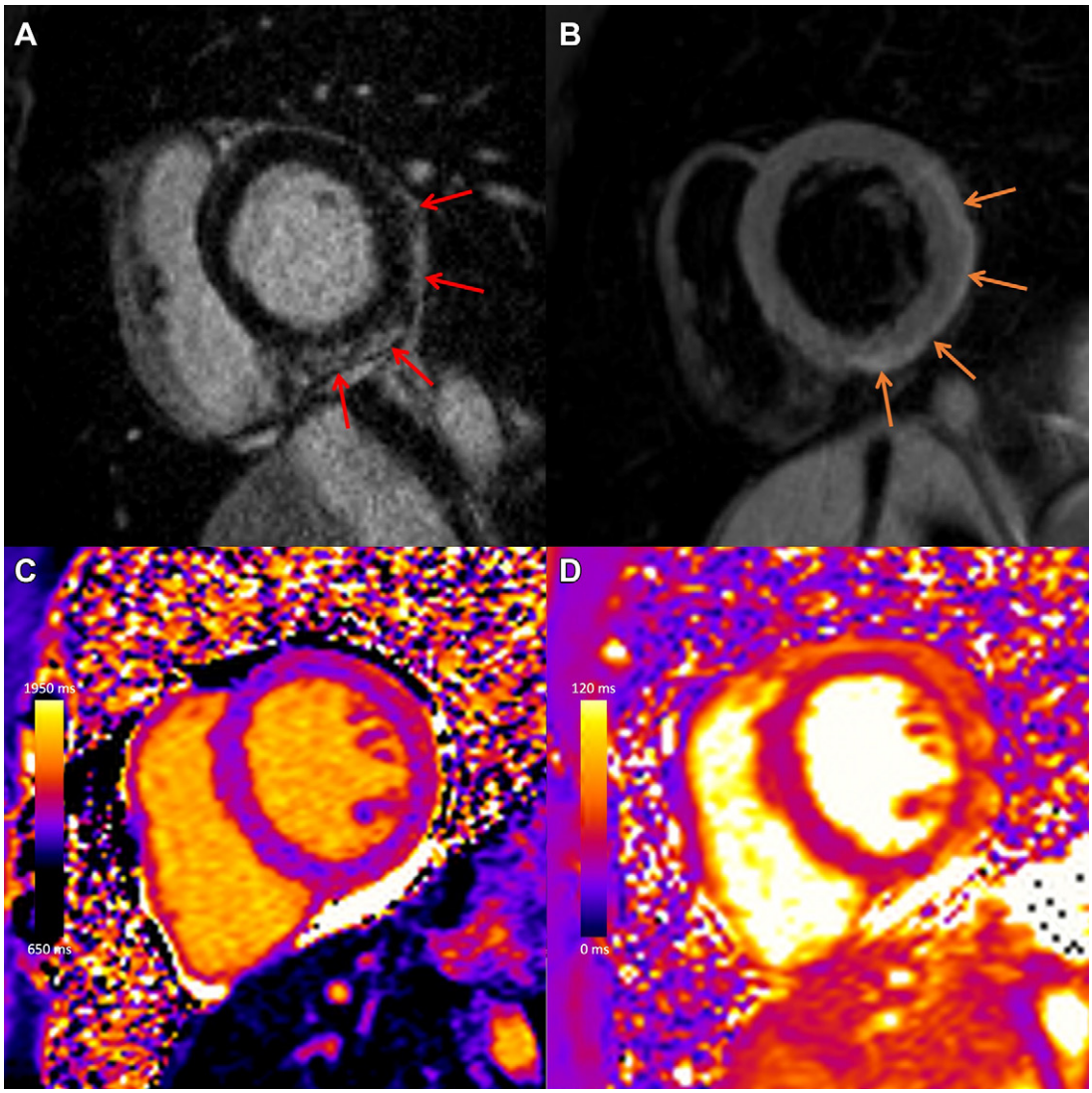

Figure 6: COVID-19 vaccine–associated myocarditis. Case example in a 27-year-old man with myocarditis 3 days following COVID-19 vaccine administration. Images from cardiac MRI performed at 1.5 T demonstrate subepicardial late gadolinium enhancement at the **(A)** basal to mid anterior lateral, inferior lateral, and inferior wall (red arrows), with **(B)** corresponding high T2 signal (orange arrows), **(C)** high regional native T1 (1173 msec), and **(D)** high regional native T2 (59 msec) on short-axis images.

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