Systemic Vasculitis: An Underestimated Cause of Heart Failure—Assessment by Cardiovascular Magnetic Resonance

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Cardiovascular manifestations in systemic vasculitis include initially silent cardiomyopathy due to either ischemic or inflammatory causes. The combination of vasculitis and cardiomyopathy is associated with a poor prognosis. Early treatment with immunosuppressants in conjunction with appropriate cardiac pharmacotherapy is considered important and has dramatically improved prognosis. Cardiovascular magnetic resonance, due to its nonionizing, noninvasive evaluation of the cardiovascular system, can be of great value in the diagnosis, follow-up, and treatment of patients with systemic vasculitis.

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KEY WORDS

Cardiovascular magnetic resonance • Systemic vasculitis • Coronary artery disease • Myocardial ischemia • Myocardial inflammation • Myocardial fibrosis

The term *vasculitis* refers to a heterogeneous group of diseases characterized by inflammation and fibrinoid necrosis of the vascular wall. The vasculitis may be primary in origin, without any identifiable cause, or it may be secondary due to infection, malignancy, or autoimmune disease. There is evidence that the presence of vasculitis can accelerate atherosclerosis in various autoimmune diseases including connective tissue diseases (CTDs), such as rheumatoid arthritis (RA), systemic sclerosis (SSc), sarcoidosis, and systemic lupus erythematosus (SLE). This article focuses on vasculitis due to CTDs, their possible evolution to heart failure (HF), and the role of cardiovascular magnetic

resonance (CMR) to diagnose and guide appropriate treatment in these patients.

The classification of systemic necrotizing vasculidites, according to the Chapel Hill Consensus Conference,[1] depends on the predominant type of vessels affected. They can involve the aorta and its major branches, as in giant cell arteritis and Takayasu's arteritis (TA), medium-sized vessels, as in polyarteritis nodosa (PAN) and Kawasaki disease (KD), and small vessels (arterioles, capillaries, and venules), as in Wegener granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and mixed cryoglobulinemic vasculitis (MCV). WG, CSS, MPA, and necrotizing glomerulonephritis are characterized by the presence of antineutrophil cytoplasmic antibodies (ANCAs) and for this purpose are considered as ANCA-related vasculidites.

The vasculidites that occur during the course of autoimmune diseases usually affect small-sized vessels as in SLE, SSc, and Sjögren syndrome. When vasculitis occurs during the course of RA, both small- and medium-sized arteries can be involved, mimicking polyarteritis nodosa.[2]

Cardiac manifestations can occur with varying frequency in these diseases, depending on the type of vasculitis; although they are rarely predominant, they can be life threatening. Each cardiac tissue can be affected during the course of vasculidites. However, all the cardiovascular manifestations of vasculidites should be distinguished from those that can take place as a consequence of other organ involvement or treatment side effects. Long-term therapy with corticosteroids and immunosuppressants, such as cyclophosphamide, which are frequently used in the treatment of different vasculitis, hypertensive cardiomyopathy, and traumatic perforation related to hemodynamic evaluation, can cause additional heart involvement.[3]

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Pathogenesis

The pathogenesis of these vasculidites involves cell-mediated inflammation, immune complex (IC)-mediated inflammation, and ANCA-mediated inflammation. Cell-mediated inflammation is a characteristic of giant cell arteritis. IC- and ANCA-mediated inflammation was identified in the necrotizing vasculidites that affect medium-sized and small blood vessels. Endothelial cell activation via autoantibody or IC binding is a common pathogenic pathway in systemic vasculitis associated with RA and SLE. Systemic vasculitis occurs in most CTDs and there is evidence that inflammation is the link between vasculitis and accelerated atherosclerosis in these patients.[4-12]

Clinical Presentation

HF during the course of vasculitis can be due to different mechanisms including the following:

1. Vasculitis-specific myocarditis that can lead to a dilated cardiomyopathy;
2. Coronary vascular inflammation with resultant ischemic cardiomyopathy; and
3. Infrequently, valvular lesions.

The incidence of vasculitis-related myocarditis varies widely. However, it has been reported that up to 78% (mean = 25%-30%) of patients with polyarteritis nodosa had evidence of myocarditis.[13-15] The origin of myocarditis during vasculitis has a multifactorial origin. It can be due to necrotizing vasculitis involving myocardial arterioles and venules, eosinophilic infiltration, especially in CSS,[15] and associated fibrosis as a result of persistent inflammation.

The inflammation of the coronary arteries is expressed in the form of coronary arteritis and manifested clinically as aneurysms, thromboses, dissections, and stenoses. All these coronary lesions may lead to myocardial infarction (MI) and possibly contribute to HF. Coronary involvement was documented by autopsy in 50% of patients with polyarteritis nodosa (PAN).[16] However, KD is the vasculitis with the highest frequency of coronary arteritis, with 20% to 25% of patients developing aneurysms before immunoglobulin administration.[17]

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Valvulitis, although rare, may lead to valve distortion with related hemodynamic consequences and HF, despite immunosuppressive treatment.[18]

PAN

Cardiac involvement in PAN was reported in 10% to 78% of patients. Left ventricular (LV) HF is the predominant finding and is mainly

due to coronary arteritis. Schrader and colleagues[16] found that 50% of 36 autopsied PAN patients had coronary arteritis and 8% had extensive areas of MI. However, clinical angina was rare, observed in only 2% to 18% of patients. In addition, sinus tachycardia, arrhythmias, and conduction disorders have been observed in 2% to 19% of such patients due to arteritis involving the sinus node or other components of the conduction system.[19]

KD

Coronary artery aneurysms or ectasia develop in 15% to 25% of untreated children and may lead to ischemic heart disease or sudden death.[20-22] However, approximately 50% of the children with coronary aneurysms during the acute phase of the disease have normal-appearing vessels examined by angiography 1 to 2 years later.[23]

In addition, 50% to 70% of patients may develop myocardial inflammation 2 to 4 weeks after the onset of symptoms. The clinical course of myocardial inflammation is manifested by mild to severe LV dysfunction. Congestive HF is due either to ischemic heart disease (significant coronary artery stenosis or occlusion) or to myopericarditis.[19]

WG

Cardiac involvement has been reported in 30% of autopsied patients with WG.[24,25] Coronary arteritis, usually silent, occurs in 50% of patients with WG who have cardiac involvement (Figure 1), myocarditis in 25%, valvulitis in 21%, and MI in 11%.[24,25] The aortic and mitral valves have been reported to be the most commonly affected during the course of WG.[25] Aortic valve regurgitation is usually due to distortion and thickening of aortic cusps or cusp perforation, due to local vascular necrosis during the active phase of WG, or due to late dilatation of the aortic root.[25]

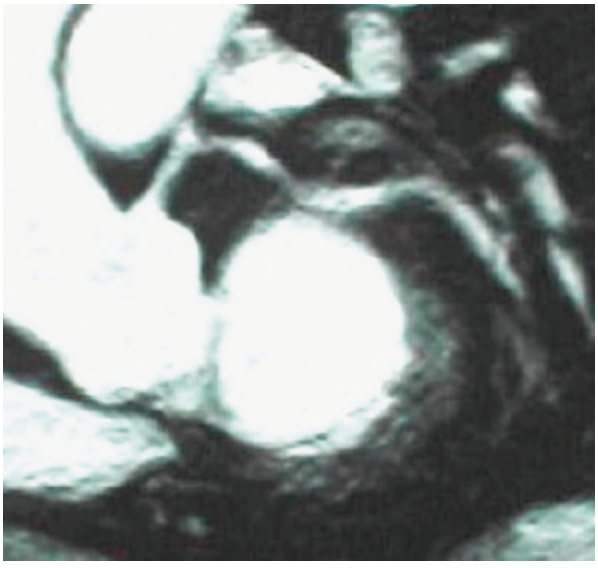

Figure 1. Ectatic left anterior descending artery in a patient with Wegener granulomatosis.

by granulomatous infiltration of the myocardium. Myocarditis can lead to dilated cardiomyopathy with intraventricular thrombi. It is characterized not only by fibrosis, but also by an active inflammatory process and may influence therapeutic decisions, even if CSS is considered in full clinical remission.[26]

Morgan and associates documented cardiac valve involvement, although rare, as a consequence of subendocardial fibrosis.[27]

MPA

In a recent analysis of 85 patients with MPA, 17% developed HF, with a higher incidence of subclinical MI than in other small vessel vasculidites.[28] MPA with lung and kidney involvement appears to be associated with perinuclear ANCA, whereas heart involvement may be more frequent in ANCA-negative patients.

Cardiac involvement is a frequent finding, present in 60% of patients with CSS, and is responsible for 48% of deaths in these patients.

CSS

Cardiac involvement is a frequent finding, present in 60% of patients with CSS, and is responsible for 48% of deaths in these patients.[15] Cardiomyopathy is due to vasculitis-related ischemia affecting small myocardial vessels and coronary arteries, or myocardial eosinophilic infiltration followed by fibrosis or, more rarely,

MCV

Congestive HF due to silent MI may be seen in up to 30% of patients with MCV. It is currently attributed to hepatitis C virus infection in more than 80% of cases.[29]

TA

Traditionally, HF in this disease is the result of aortic regurgitation, inadequately treated hypertension, coronary artery disease, and pulmonary vascular involvement. However, in some cases, LV dysfunction was documented without associated hypertension, valvular lesions, or coronary artery disease. In these cases, the coexistence of myocarditis with subclavian stenosis has been already reported.[30-33]

The combination of inflammatory myocarditis and TA seems to be common in certain races or geographic regions. Previous studies reported that a lymphocytic infiltration consistent with myocarditis was present in approximately 50% of cases in India. TA myocarditis is the result of cytotoxicity and can be successfully treated by immunosuppressive therapy.[32,33]

Vasculitis in RA and SLE

Vasculitis is a known complication of RA and usually occurs several years after the initial onset of the disease. Rheumatoid vasculitis can be severe and, if so, should be treated with corticosteroids and cyclophosphamide. However, despite such treatment, the outcome is generally worse than in the majority of vasculitides.[34] Patients with RA are at twice the risk for developing coronary artery disease,[35,36] as reflected by the high incidence of MI (frequently unrecognized), congestive HF,[37] and sudden cardiac death.[35] Inflammation seems to be the key link between RA and accelerated atherosclerosis as determined by the correlation between ultrasound measured intima-media thickness and both erythrocyte sedimentation rate and C-reactive protein.[38] In addition, corticosteroids may also promote atherosclerosis.[39]

The vasculitis in SLE is similar to that in RA; however, SLE patients have an even greater incidence of atherosclerotic plaque in carotid arteries,[40,41] more commonly observed coronary artery calcification,[42] and higher frequency of MI and stroke compared with healthy populations (Figure 2 and Figure 3). Although risk factors for atherosclerosis in SLE patients are similar to those in RA patients, there are additional SLE-related risk factors, such as autoantibodies to endothelium, high-density lipoprotein, and phospholipids, as well as dyslipidemia.[43] The enhanced frequency of circulating ICs, activated complement products and nephritis are additional SLE-related risk factors.[44,45]

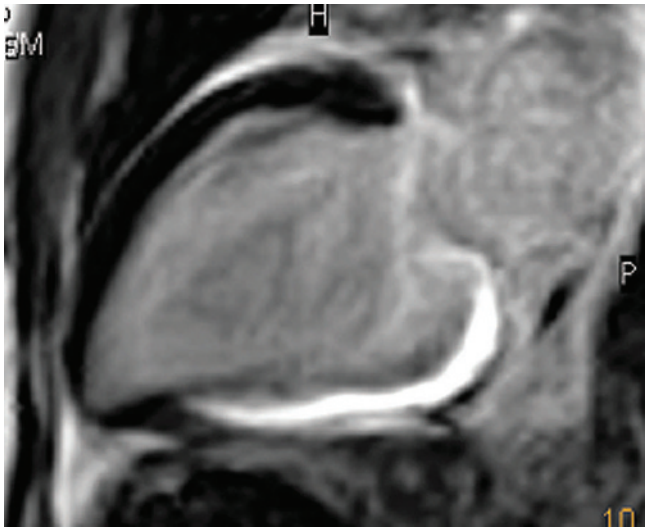

Figure 2. Transmural inferior myocardial infarction in a patient with systemic lupus erythematosus.

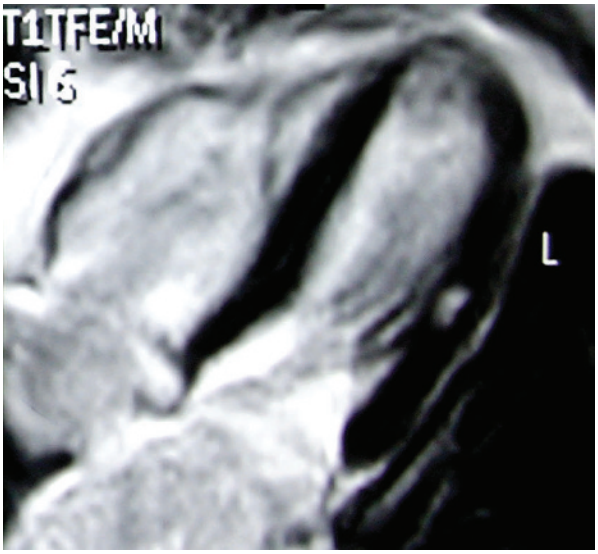

Figure 3. Intramyocardial lesion in the lateral left ventricular wall due to vasculitis in a patient with rheumatoid arthritis.

Therapeutic Strategies in Vasculitis

Clinical management of vasculitis associated with CTDs requires a multifaceted approach to detect the underlying disease, the vasculitis, and its severity. In addition, there may be a need to properly treat symptomatic manifestations. Overall, the aim of treatment is to control disease, prevent relapse, and increase event-free survival. Currently, corticosteroids and immunosuppressives such as cyclophosphamide are the mainstay for the treatment of vasculitis.[27,28] This strategy has also proved effective in vasculitis secondary to RA.[19] Furthermore, controlling disease activity in RA with methotrexate has led to a substantial reduction of fatal acute MI.[46] In addition, treatment of cardiac complications, using nitrates for ischemia, statins for hyperlipidemia, and angiotensin-converting enzyme inhibitors to diminish inflammation and prevent LV dysfunction, should be also considered in the management of these patients.

Role of CMR in the Diagnosis of Vasculitis

CMR, a noninvasive, nonionizing imaging approach, can be of substantial value in the assessment of vasculitis, offering a way to detect all of the affected cardiac structures. CMR allows assessment of cardiac volumes, systolic and diastolic cardiac function, the coronary arteries, and the detection of myocardial fibrosis, inflammation, and perfusion.

Measurement of Ventricular Volumes and Ejection Fraction

CMR can measure ventricular volumes and ejection fraction noninvasively and without a contrast agent. In a direct comparison of CMR versus echocardiography for reproducibility, it has been shown that, for a power of 80% and a *P* value of .05, the sample size required would be 505 patients for validation using two-dimensional echocardiography, and only 14 patients for CMR.[47] Although echocardiography is relatively inexpensive, more widely available, and can be performed at the bedside, CMR results are more reproducible and provide more accurate results. Accordingly, CMR is the optimal technology for diagnosis, prognostication, and follow-up.

Coronary Vessels

Three-dimensional, non–contrast-enhanced, free-breathing coronary magnetic resonance angiography (CMRA) facilitates the visualization of the vast majority of the coronary arteries.[48] However, CMRA can achieve neither the resolution of radiographic angiography for grading of coronary artery stenoses, nor the resolution of CT coronary angiography to identify coronary artery calcification. The first multicenter CMRA trial using navigator techniques showed a high sensitivity for the detection of coronary artery disease (95%). Although the specificity was relatively low (34%), its negative predictive value for three-vessel disease was high (90%), allowing the exclusion of high-risk patients scheduled for surgery. However, accuracy was too low for a general clinical indication.[48-50] Two recently published studies using more sophisticated techniques showed a sensitivity of 78% and 82%, a specificity of 91% and 90%, and a predictive accuracy of 89% and 87%, respectively.[51,52]

Comparative analyses have previously demonstrated that CMRA is of equal value with radiographic angiography in patients with KD[53] and in the evaluation of ectatic vessels[54] and also can be used as a noninvasive diagnostic tool in the assessment of vasculitis.[55] CT CMRA has the advantage of requiring no exposure to ionizing radiation and no usage of iodinated contrast agents. This is of special importance in vasculitis patients who have impaired renal function.

Fibrosis

The addition of contrast-enhanced magnetic resonance imaging (MRI) has the advantage to accurately detect small areas of myocardial scar that are undetectable by other imaging techniques.[56] Contrast-enhanced MRI has been demonstrated to be in agreement with histopathology and to distinguish reversible from irreversible myocardial injuries, as well as identify their subendocardial or transmural localization.[57,58] However, gadolinium contrast agents have risks related to the potential to develop nephrogenic fibrosing dermopathy or nephrogenic systemic fibrosis, particularly in patients with renal insufficiency.[59]

Recently, the application of late gadolinium enhancement (LGE) for the detection of myocardial necrosis has been described in vasculitis[53-55] and SLE.[60,61] Importantly, the LGE findings in vasculitis do not present the typical image pattern found in ischemic heart disease (subendocardial or transmural lesions that relate to the territory supplied by the occluded arteries). In contrast, the pattern of lesions is mainly intramyocardial or subepicardial and rarely subendocardial. Such patterns can be found in any area of myocardium, do not depend on the distribution of coronary artery supply, and are usually located in the inferior or inferolateral wall of the LV, similar to the pattern associated with viral myocarditis. In addition, the possibility of coexistent CAD or MI should always be considered when evaluating vasculitis patients. Furthermore, CMR offers the opportunity to detect silent cardiac involvement commonly found in vasculitis and small subendocardial infarctions undetected by other imaging techniques.[56]

Myocardial Inflammation

CMR can easily visualize the entire myocardium and it is ideal for a patchy process like myocarditis. It is also very useful for the evaluation of changes in tissue composition, which are associated with myocarditis. CMR contributes to the diagnosis of myocarditis using three types of images: T2-weighted images, early T1-weighted images obtained during the first minute after contrast agent administration, and delayed enhanced images (LGE) taken 15 minutes after the injection of contrast agent. The pooled data concerning the detection of viral myocarditis showed that, if all sequences can be performed and two or more of the three tissue-based criteria are positive, myocardial inflammation can be predicted or ruled out with a diagnostic accuracy of 78%. These findings indicate

that a positive CMR study result specific and therefore very helpful for identifying inflammation.[62]

Until now, CMR has been successfully used for the evaluation of myocardial inflammation in vasculidites,[26,63-65] SLE,[65-67] and TA.[33] Consistent with our experience in clinical practice, CMR has been able to detect myocardial inflammation in SLE and CSS patients with subtle clinical symptoms and a normal echocardiogram. In a recent study, 32 patients with CSS in remission without known cardiac involvement were compared with control subjects using clinical evaluation, electrocardiography, echocardiography, and cardiac MRI. Cardiac MRI detected cardiac abnormalities (wall motion and presence of LGE) in 62% of CSS patients. The absence of symptoms or electrocardiographic abnormalities did not exclude cardiac involvement with CSS because abnormal clinical and imaging findings were detected in 38% of these patients at the time of cardiac MRI.[68]

Myocardial Perfusion

CMR can delineate underperfused regions associated with myocardial ischemia by using the first pass of a bolus of gadolinium contrast agent (first-pass gadolinium)[69,70] after the administration of a vasodilator-stress (most commonly using adenosine). The spatial resolution of CMR myocardial perfusion imaging of 2 to 3 mm is superior to that of other imaging modalities, such as radionuclide methods, so that subendocardial ischemia can be more reliably identified.[69,70] Recently, myocardial perfusion has been studied in SLE, RA, and SSc using CMR.[71-73]

Conclusions

Systemic vasculitis can affect the heart, inducing either an ischemic or an inflammatory process. Early diagnosis and treatment with immunosuppressive and cardiac medication can protect vasculitis patients from further heart complications and development of HF.

The capability of CMR to offer multiple diagnostic perspectives in one examination without the use of ionizing radiation can contribute to early diagnosis, treatment, and reduction of HF in systemic vasculitis. However, the lack of availability and expertise, and also the high cost, do not always justify the routine application of CMR. Nevertheless, according to recent data, there is a high percentage of silent heart involvement during the course of vasculitis that runs undetected by the routine echocardiographic evaluation.[64,65,71-73] These patients, if undetected and left untreated, can substantially increase the cost of health care. With this in mind, the application of CMR should be considered the only noninvasive technique for early detection of cardiac involvement which can possibly dictate a new therapeutic approach for the prevention of HF in vasculitis. ■

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MAIN POINTS

- Systemic vasculitis can affect the heart by inducing either an ischemic or an inflammatory process. Early diagnosis and treatment with immunosuppressive and cardiac medication can protect vasculitis patients from further heart complications and development of heart failure (HF).
- The capability of cardiovascular magnetic resonance (CMR) to offer multiple diagnostic perspectives in one examination without the use of ionizing radiation can contribute to early diagnosis, treatment, and reduction of HF in systemic vasculitis. However, the lack of availability and expertise, and also the high cost, do not always justify the routine application of CMR.
- HF during the course of vasculitis can be due to different mechanisms including: vasculitis-specific myocarditis that can lead to dilated cardiomyopathy, coronary vascular inflammation with resultant ischemic cardiomyopathy, and, infrequently, valvular lesions.
- CMR should be considered the only noninvasive technique for early detection of cardiac involvement that can possibly dictate a new therapeutic approach for the prevention of HF in vasculitis.

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