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EDITORIAL COMMENT

Cardiac Involvement in Connective Tissue Disorders

Terra Incognita*

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In this issue of *JACC: Case Reports,* Motwani et al. (1) present a clinical case of a patient with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) with aortic valve thickening and regurgitation, aortopathy, and inflammatory myocardial injury. The case illustrates the potential of cardiovascular magnetic resonance (CMR) to visualize multiple cardiovascular complications in connective tissue disorders.

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Connective tissue disorders comprise a heterogeneous form of autoimmune rheumatic diseases, with SLE being the most common in the developed world. Cardiac involvement in patients with SLE and APS is a result of a complex interplay between traditional risk factors and dysregulation of autoimmunity (2). SLE may be associated with coronary artery disease (CAD), myocarditis, pericarditis, valvular heart disease, conduction abnormalities, heart failure, and pulmonary hypertension. Various clinical phenotypes can coexist in a single patient, as has been elegantly demonstrated by Motwani et al. (1).

Because of its high availability, portability, low cost, lack of ionizing radiation, and great expertise with its use among cardiologists, echocardiography remains the most common noninvasive imaging modality for investigating patients with suspected or confirmed SLE. However, as highlighted and recommended by international experts, CMR should be considered as a potentially preferable diagnostic tool in connective tissue disorders (3). CMR has many advantages, especially unrestricted tomographic and functional imaging and tissue characterization. In patients with SLE and APS, cardiovascular complications may be clinically silent. Therefore, advanced imaging techniques such as CMR are valued in these patients. The role of CMR in SLE and APS is summarized in **Table 1**.

MYOCARDIAL AND PERICARDIAL INFLAMMATION

Myocardial inflammation is a hallmark of SLE and has been linked to myocardial dysfunction and heart failure in patients with SLE (2). Cardiac injury is accelerated through bouts of active disease. However, much of this process can remain subclinical, and the diagnosis therefore is often challenging. Yet detection of early myocardial changes is of paramount importance because it may guide preventive interventions.

CMR offers a unique noninvasive tool to characterize myocardial tissue (4). Edema (increased water content) is a sign of tissue inflammation and can be depicted by a regional or global increase in myocardial or pericardial T_2 signal intensity on T_2-weighted images or by increased T_2 relaxation times on T_2 mapping. Nonischemic myocardial injury can be demonstrated by the presence of late gadolinium enhancement (**Figures 1A to 1D**), as well as a regional or global increase in native T_1 relaxation time or extracellular volume. Although each parameter may indicate myocardial edema or inflammation, a combination of positive T_2 and T_1 tissue property-based markers increases the specificity of the technique. In addition, pericardial inflammation, characterized

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TABLE 1 Role of CMR in Detecting Cardiovascular Complications in SLE and APS

Cardiovascular Complication	Parameter Evaluated	CMR Techniques
Myocardial or pericardial inflammation	Tissue injury (edema, inflammation, necrosis, fibrosis), pericardial effusion	T_2-weighted imaging, LGE, T_2 mapping, T_1 mapping, ECV
Coronary artery disease	Ventricular volumes, ejection fraction, regional systolic function, myocardial strain, stress and rest myocardial perfusion, tissue injury (edema, necrosis, scar)	Cine imaging, tissue tracking techniques, T_2-weighted imaging, T_2 mapping, vasodilator stress CMR, dobutamine stress CMR, LGE, T_1 mapping
Heart failure	Ventricular volumes, ejection fraction, regional systolic function, myocardial strain	Cine imaging, tissue tracking techniques
Valvular heart disease	Valve morphology, mechanism of dysfunction, quantification of lesion (regurgitation) severity, assessment of great vessels	Cine imaging, phase-contrast velocity-encoded imaging, MRA, 4D flow

APS = antiphospholipid syndrome; CMR = cardiac magnetic resonance; ECV= extracellular volume; LGE = late gadolinium enhancement; MRA = magnetic resonance angiography; SLE = systemic lupus erythematosus.

by pericardial effusion and/or late gadolinium enhancement of the pericardium, and left ventricular dysfunction in areas corresponding to myocardial inflammation can provide supportive signs to establish the correct diagnosis.

CORONARY ARTERY DISEASE

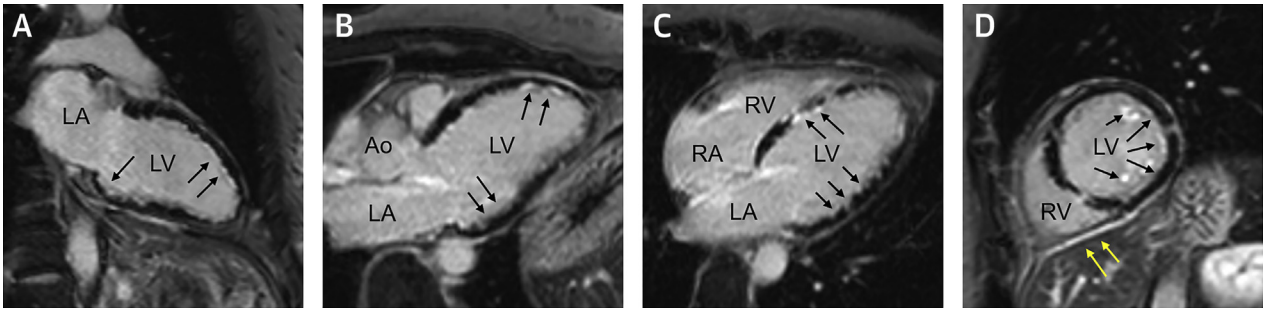
CAD is an important cause of mortality of patients with SLE (5). Cardiovascular morbidity in SLE is as frequent as in age- and sex-matched patients with type 1 diabetes mellitus (6). Traditional cardiovascular risk factors, such as hypertension, dyslipidemia, and insulin resistance, are more prevalent in SLE, but they are not sufficient to explain the magnitude of the CAD burden (7). Immune dysregulation, genetic predisposition, and immunosuppressive treatment may be contributing factors. Lupus anticoagulant and anti-β_2-glycoprotein I, associated with APS, are recognized risk factors for myocardial infarction in patients with SLE (2).

CMR can help to detect the presence of CAD. An infarct-type late gadolinium enhancement pattern (subendocardial enhancement with a variable range of transmural involvement, present in a coronary artery perfusion territory) is very specific for a previous myocardial infarction. Left ventricular remodeling and regional functional impairment strengthen the suspicion of CAD. Vasodilator or dobutamine stress CMR can help to identify myocardial ischemia. Apart from obstructive CAD, myocardial ischemia in patients with SLE and APS can be caused by microvascular dysfunction. In a recent study, vasodilator stress CMR test results were positive in 44% of patients with SLE, anginal chest pain, and no obstructive CAD, thus implying a high prevalence of microvascular angina (8).

HEART FAILURE

Heart failure in SLE is secondary to myocardial infarction or chronic myocardial inflammation. CMR cine imaging is considered a reference standard for the quantitative evaluation of left and right ventricular volumes, myocardial mass, and global and regional myocardial function. Left ventricular and right ventricular myocardial strain can be assessed using any tissue tracking techniques such as myocardial tagging, feature tracking, strain-encoded (SENC) imaging, or displacement-encoding (DENSE) imaging.

FIGURE 1 Inflammatory Myocardial Injury in SLE



A 41-year-old woman with a medical history of systemic lupus erythematosus (SLE) presented with symptoms of acute heart failure. Cardiovascular magnetic resonance demonstrated focal subendocardial late gadolinium enhancement **(black arrows)** in almost the entire left ventricle (LV), including the papillary muscles (suggestive of vasculitis) and late gadolinium enhancement of the pericardium **(yellow arrows, D)**. There was no evidence of acute regional or global myocardial or pericardial injury on T_2-weighted images. **(A)** A 2-chamber view. **(B)** A 3-chamber view. **(C)** A 4-chamber view. **(D)** A short-axis midventricular view. Ao = aortic root; LA = left atrium; RA = right atrium; RV = right ventricle.

VALVULAR HEART DISEASE

Valvular complications are common in both SLE and APS (2). Valve thickening and vegetation, also known as Libman-Sacks endocarditis or sterile endocarditis, are frequent cardiac manifestations. The mitral valve is mainly affected, followed by the aortic valve (9). Valvular involvement usually does not cause clinically overt valvular heart disease, but in some cases it can lead to extensive valve deformity and dysfunction. The predominant functional abnormality is regurgitation; stenosis is rare (9). Libman-Sacks lesions may also predispose patients to bacterial endocarditis.

Although echocardiography, especially using the transesophageal approach, is the preferred method to evaluate valve morphology and mechanisms of regurgitation, CMR can assess morphological and functional changes associated with valvular heart disease as well. In particular, CMR offers an incremental value in the assessment of regurgitation severity. Phase-contrast velocity-encoded imaging allows for direct (aortic valve) or indirect (mitral valve) quantification of regurgitation severity. CMR plays a similarly important role in the assessment of the great vessels, which are less frequently affected in patients with SLE or APS but can be precisely visualized using magnetic resonance angiography. Novel techniques, such as 4D flow, further assert the role of CMR in valvular heart disease.

CONCLUSIONS

The wide range of potential cardiovascular complications in connective tissue disorders requires a multimodality imaging approach. CMR, with its broad imaging capabilities, is a valuable diagnostic tool. Cardiovascular complications should be diagnosed at an early stage to implement appropriate therapeutic interventions and prevent late complications.

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