**EDITORIAL COMMENT**

**Coronary Microvascular Dysfunction in Systemic Lupus Erythematosus Identified by CMR Imaging***

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Systemic lupus erythematosus (SLE) is a multisystem, autoimmune, connective tissue disorder and is one of the strongest known risk factors for atherosclerosis and coronary artery disease (CAD) (1). The range of cardiovascular disease in SLE includes atherosclerosis, vascular inflammation, Raynaud’s phenomenon, endothelial dysfunction, and a procoagulant tendency associated with antiphospholipid antibodies. It was first noted in 1976 that there is a bimodal pattern of death in SLE. An early peak (within the first year of diagnosis) was related to nephritis and sepsis. A later peak (at around 8 years after diagnosis) was related to premature myocardial infarction (2). The incidence of coronary artery disease (CAD) is over 7 × greater than in healthy controls, even after matching for cardiovascular risk factors, with a relative risk of death from myocardial infarction of 17 (3). In women between 35 and 44 years of age with SLE, the incidence of myocardial infarction is more than 50 × greater than in the Framingham dataset (4). The degree of SLE disease activity in the previous year correlates with index events of CAD (5), consistent with the paradigm of atherosclerosis as a disease of vascular inflammation (6).

Patients with SLE frequently report chest pain. As in the non-SLE population, there is a wide range of possible diagnoses, and cardiac testing, often involving invasive angiography, is frequently performed because of the high incidence of CAD. When this is normal, an alternative diagnosis, such as pleuritis or musculoskeletal chest pain, may be made. Some of these patients may have cardiac syndrome X (CSX) (7), which is defined as anginal chest pain, an exercise test that is positive for ischemia, but normal coronary angiography (8). Cardiac magnetic resonance (CMR) demonstrates that 90% of CSX patients have myocardial perfusion abnormalities by stress CMR, indicating that CSX is associated with coronary microvascular dysfunction (9). CMR is a well-established technique for myocardial perfusion imaging. It offers superior spatial resolution to single-photon emission computed tomography without exposing the patient to ionizing radiation. There is little previous literature on CSX and coronary microvascular dysfunction in patients with SLE.

The paper by Ishimori et al. (10) in this issue of *JACC* describes the use of stress CMR perfusion in a cohort of 20 SLE patients with chest pain and no obstructive CAD on coronary computed tomography angiography (CTA). The authors’ hypothesis is that “chest pain in SLE patients without obstructive CAD is due to myocardial ischemia potentially due to microvascular coronary dysfunction.” CMR is a well-established technique for myocardial perfusion imaging. It offers superior spatial resolution to single-photon emission computed tomography without exposing the patient to ionizing radiation. There is little previous literature on CSX and coronary microvascular dysfunction in patients with SLE.

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The number of patients is typical for an imaging study in this area. The gadolinium adenosine-stress first-pass perfusion CMR technique used is the normal

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sequence in routine clinical use. Qualitative and quantitative analysis was performed, and patients with established atherosclerosis were excluded.

However, some caveats are needed for the applicability of these results. By design, all subjects were female. This was a relatively healthy SLE population, with a low to moderate level of disease activity, and, in particular, there were relatively few smokers. This may explain the coronary CTA results in which only 1 patient had a coronary artery calcium score >0 and only 2 patients had any coronary artery plaque at all. This is in contrast to other studies that show a much higher prevalence of CAD. For example, a computed tomography study in 65 SLE patients with no history of CAD found coronary artery calcification in 31%, with a mean coronary artery calcium score of 68.9 (11). Likewise, a single-photon emission computed tomography study showed myocardial perfusion abnormalities in 35% of women with SLE with no history of CAD (12). Hence, no patient had evidence of myocardial scarring in the late phase after gadolinium contrast, which differs from our experience in the inflammatory arthritides (13).

Importantly for a study of chest pain, the patients' symptomatology is not clearly outlined. Some patients appear to have had anginal chest pain, whereas others had less typical angina chest pain. Although all patients underwent coronary CTA, no patient had an exercise test; therefore, this was a study of female SLE patients with typical and atypical anginal chest pain, which is not identical to the strict diagnosis of CSX. This might explain why only 44% of patients had myocardial perfusion defects, half the prevalence previously reported in CSX (7).

Recent work using positron emission tomography demonstrated reduced coronary flow reserve in SLE patients without significant CAD or traditional risk factors for CAD. This marker of coronary microvascular dysfunction may be abnormal due to prolonged vascular inflammation in SLE. Interestingly, in 28% of their patients, these authors noted ischemic electrocardiographic changes with adenosine stress, similar to CSX (14). A study of young SLE patients with no history or other risk factors for CAD showed that coronary flow reserve as assessed by transthoracic echocardiography was significantly reduced compared with healthy controls (15). This confirms in the coronary circulation what has already been demonstrated in the brachial artery, that SLE patients have evidence of endothelial dysfunction (16). CSX is associated with endothelial dysfunction (17), and symptoms, exercise tolerance, and endothelial function in CSX have been significantly improved with statin therapy (18). The current study by Ishimori et al. (10) shows that this is relevant in SLE, given that it has already been suggested that SLE should be regarded as a coronary heart disease equivalent, in much the same way as diabetes (19).

In summary, this study using stress CMR perfusion for the first time in an SLE population shows a high burden of coronary microvascular dysfunction. We agree with the authors’ conclusion that further work in a larger SLE population is warranted to assess the scale of the problem and to move toward therapy.

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