

## Microvascular Angina: An Underappreciated Cause of SLE Chest Pain

To the Editor:

Data are accumulating that microvascular dysfunction is an unrecognized source of anginal chest pain in patients with autoimmune diseases such as systemic lupus erythematosus (SLE)<sup>1,2,3</sup>. Studies show that microvascular impairment contributes to cardiovascular disease in other autoimmune conditions such as systemic sclerosis<sup>1,2,4</sup>. Patients with SLE presenting with anginal chest pain pose a diagnostic challenge. Evaluating the role of microvascular impairment as a cause of chest pain may lead to earlier and improved management of these patients.

Chest pain and discomfort are frequently reported by patients with SLE<sup>5</sup>, the origin of which can be attributed to multiple causes, including valvular disease, conduction abnormalities, pericardial disease (pericarditis, pericardial effusion), myocarditis, pulmonary hypertension, coronary artery disease (CAD), esophageal disease, musculoskeletal manifestations (costochondritis, myofascial pain, muscle spasm), and even psychiatric illness. However, upon clinical examination, diagnostic testing is often generally negative or minimally abnormal. Normal or minimally abnormal cardiovascular findings on coronary angiography are particularly frustrating to interpret, leaving the physician puzzled about the reported chest pain<sup>6</sup>.

Anginal chest pain without flow-limiting stenosis on coronary angiography is often referred to as cardiac syndrome X (CSX)<sup>6,7,8</sup>. Patients with CSX are predominantly older women and exhibit a classic triad of angina, evidence of myocardial ischemia, and normal coronary arteries<sup>7,8</sup>. Causal mechanisms that have been ascribed to CSX include microvascular coronary dysfunction (MCD), diffuse atherosclerosis, hematologic dysfunction, chronic systemic inflammation, diffuse conduit vessel vasoconstriction, myocardial ischemia, estrogen deficiency, and abnormal pain perception<sup>7</sup>. CSX is not necessarily a benign condition<sup>8</sup>. It has been reported that in these women with signs and symptoms of ischemia, the risk is elevated for cardiovascular events such as myocardial infarction, stroke, or hospitalization for unstable angina or heart failure, despite the absence of obstructive CAD compared to asymptomatic control women<sup>9,10</sup>.

The prevalence of CSX is roughly 42% in women with cardiac chest pain in the absence of obstructive CAD, and at least 1 estimate suggests that up to 58% of patients without obstructive CAD have MCD<sup>7</sup>. Adenosine cardiac magnetic resonance imaging (CMRI) is a noninvasive method that can detect stress-induced hypoperfusion in a diffuse, circumferential pattern indicating MCD. Studies have shown that an impaired endothelial-dependent vasomotor response to acetylcholine in this setting results in adverse cardiac events; further, an abnormal coronary flow reserve to intracoronary reactivity testing with adenosine is also associated with adverse cardiac outcomes in women with no obstructive CAD<sup>10,11</sup>. However, only recently has the occurrence of MCD been investigated in patients with SLE.

MCD that occurs in CSX may account for a significant proportion of the chest pain reported by patients with SLE. We investigated the presence of myocardial ischemia in 18 women with SLE who displayed anginal chest pain in the absence of obstructive CAD on coronary angiography<sup>1</sup>. Eighteen patients and 10 asymptomatic controls underwent adenosine stress CMRI and 64-slice coronary computed tomography (CT) angiography. We observed a 44% prevalence of abnormal stress myocardial perfusion in patients with SLE. Compared with controls, patients with SLE had reduced myocardial perfusion reserve index (MPRI), with SLE being a significant predictor of abnormal MPRI. Our finding is consistent with circumferential subendocardial hypoperfusion attributed to MCD in CSX, leading us to hypothesize that chest pain in patients with SLE and non-obstructive CAD may be attributable to MCD. A Japanese study of 16 consecutive SLE patients by CMRI detected perfusion defects indicating MCD in 7 patients (43.8%), although these patients were not selected on the basis of having angina<sup>3</sup>.

Our group also reported the case of a 47-year-old woman with SLE who was referred for persistent chest pain<sup>2</sup>. As often seen in these patients, she did not have obstructive CAD, as evidenced by normal CT angiography and echocardiogram. However, an adenosine stress CMRI perfusion study demonstrated nearly circumferential subendocardial hypoperfusion consistent with MCD. Again we noted that chest pain in patients with SLE, when not related to obstructive CAD, myocarditis, or pericarditis, can alternatively be caused by MCD.

As a result of this accumulation of evidence we believe that the possibility of MCD should be considered as etiologic in patients with SLE who present with anginal chest pain. This evaluation should accompany patient assessments for traditional risk factors, given the increased risk for CAD in general in these diseases. Further investigation into microvascular angina in patients with SLE is warranted. We await mechanistic investigations that could pinpoint the anatomic pathologic correlates of this potentially treatable condition; the well-recognized premature mortality and morbidity assigned to cardiac ischemia in patients with SLE<sup>12,13,14,15,16</sup> should spur us to find the answers that are relevant to our care of these patients.

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