Coronary Heart Disease

Mechanisms of Myocardial Infarction in Women Without Angiographically Obstructive Coronary Artery Disease

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Background—There is no angiographically demonstrable obstructive coronary artery disease (CAD) in a significant minority of patients with myocardial infarction, particularly women. We sought to determine the mechanism(s) of myocardial infarction in this setting using multiple imaging techniques.

Methods and Results—Women with myocardial infarction were enrolled prospectively, before angiography, if possible. Women with ≥50% angiographic stenosis or use of vasospastic agents were excluded. Intravascular ultrasound was performed during angiography; cardiac magnetic resonance imaging was performed within 1 week. Fifty women (age, 57 ± 13 years) had median peak troponin of 1.60 ng/mL; 11 had ST-segment elevation. Median diameter stenosis of the worst lesion was 20% by angiography; 16 of 42 patients (38%) undergoing intravascular ultrasound. There were abnormal myocardial cardiac magnetic resonance imaging findings in 26 of 44 patients (59%) undergoing cardiac magnetic resonance imaging, late gadolinium enhancement (LGE) in 17 patients, and T2 signal hyperintensity indicating edema in 9 additional patients. The most common LGE pattern was ischemic (transmural/subendocardial). Nonischemic LGE patterns (midmyocardial/subepicardial) were also observed. Although LGE was infrequent with plaque disruption, T2 signal hyperintensity was common with plaque disruption.

Conclusions—Plaque rupture and ulceration are common in women with myocardial infarction without angiographically demonstrable obstructive coronary artery disease. In addition, LGE is common in this cohort of women, with an ischemic pattern of injury most evident. Vasospasm and embolism are possible mechanisms of ischemic LGE without plaque disruption. Intravascular ultrasound and cardiac magnetic resonance imaging provide complementary mechanistic insights into female myocardial infarction patients without obstructive coronary artery disease and may be useful in identifying potential causes and therapies.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00798122.

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Key Words: coronary disease imaging magnetic resonance myocardial infarction

A substantial proportion of patients with myocardial infarction (MI) have no angiographically obstructive (≥50% diameter stenosis) coronary artery disease (CAD), including ≈7% to 32% of women and 6% to 12% of men.1–4 The underlying degree of CAD ranges from absolutely no detectable luminal irregularities to moderate stenosis. Several pathogenetic mechanisms of MI in the absence of obstructive CAD have been postulated, including, among others, atherosclerosis with plaque disruption that does not lead to luminal occlusion, endothelial dysfunction with the inability to augment coronary flow in response to stress, and vasospasm.5 However, the data are extremely limited. Women are less likely to display obstructive coronary lesions when presenting with all forms of ischemic heart disease, from stable chest pain to MI and fatal ischemic heart disease.6,7 There are also sex differences in morphological characteristics of the vasculature. Outward remodeling, plaque erosion, and microvascular embolization are all more common in women.6 We sought to determine the mechanisms of MI in women without obstructive CAD by examining these patients during their index admission using intravascular ultrasound (IVUS) to determine the presence and extent of plaque and occult plaque disruption. Cardiac magnetic
resonance imaging (CMR) was performed within 1 week to determine the presence and pattern of myocardial injury.

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Methods
The study was approved by the New York University School of Medicine Institutional Review Board. All patients provided informed consent.

Patient Population
Patients were eligible for enrollment if they were women ≥18 years of age who presented with acute MI and did not have any lesion with ≥50% diameter stenosis or evidence of plaque rupture on coronary angiography at NYU Langone Medical Center or Bellevue Hospital Center. The definition of MI was based on ischemic symptoms with the elevation and fall of troponin, with or without ECG changes, per the universal definition of MI. Cardiac troponin I was measured in the clinical laboratories (VITROS immunodiagnostic assay, Ortho Clinical Diagnostics, Rochester, NY; 99th percentile, 0.034 ng/mL). Patients with troponin elevation caused by heart failure, hypertensive crisis, or chronic kidney disease were not included. The target population was women with MI who were clinically referred for angiography. Exclusion criteria were known obstructive CAD based on prior angiography or revascularization, contraindication to study procedures, and recent use of vasospastic agents such as cocaine or ergot alkaloids (≤2 weeks). Patients provided informed consent before angiography but were excluded from further participation if the angiogram showed ≥50% stenosis of a major epicardial vessel, coronary dissection, or excessive tortuosity that, in the opinion of the operator, increased the risk of IVUS.

Angiographically eligible patients underwent IVUS at the time of angiography and CMR within 7 days of angiography. A small subset of patients who could not be approached for consent until after angiography because of logistic issues did not undergo concomitant IVUS (n=8). In these cases, only CMR was performed. Demographic, ECG, left ventricular (LV) function, and laboratory data were collected. Severity of stenosis was determined by visual assessment by experienced angiographers. Left ventricular wall motion and ejection fraction were obtained by echocardiography, angiography, or CMR.

Women suspected to have takotsubo cardiomyopathy were included if they met eligibility criteria. Takotsubo cardiomyopathy was considered to be present when there was a transient mid LV wall motion abnormality with or without apical involvement extending beyond a single epicardial vascular territory in the absence of myocarditis or pheochromocytoma.

Intravascular Ultrasound
Patients who met angiographic eligibility criteria underwent IVUS with a standard clinical scanner (Boston Scientific Corp/SCIMED, Natick, MA) consisting of a rotating 40-MHz transducer within a 3.2F imaging sheath. The goal of IVUS was to image at least the proximal 40 mm of the vessel deemed by the angiographer to be the most likely culprit vessel (based on ECG, results of any wall motion studies, and the angiogram itself) and at least 1 other major epicardial vessel, using automated pullback. When a culprit artery could not be identified or if the right coronary artery was not suspected as a culprit, the left anterior descending (LAD) and left circumflex arteries were imaged. Manual advancement and withdrawal of the IVUS probe were used if additional images were needed to fully characterize any areas of the vessel.

Images were interpreted by an independent core laboratory (Cardiovascular Imaging Research Core Laboratory, University of British Columbia) for determination of plaque rupture, ulceration/erosion, thickness and presence/absence of thrombus, dissection, and calcification. Ruptured plaque was defined according to the published standard as a plaque ulceration with a tear detected in the fibrous cap, typically with a dissection into the plaque. Ulceration was defined as a recess in the plaque beginning at the luminal-intimal border, typically without enlargement of the external elastic lamina compared with the reference segment and without dissection into the plaque. Contrast injections were used as needed to prove and define the communication point. These definitions have very high reproducibility (99%). Maximal thickness >0.5 mm was considered abnormal.

Qualitative parameters (rupture, ulceration, thrombus, dissection) were assessed by 2 independent, experienced readers at the core laboratory and verified by a cardiologist. Parameters were also reviewed by a cardiologist (H.R.R.) board certified in cardiovascular ultrasound at the enrolling center. The core laboratory was blinded not only to clinical, ECG, laboratory, angiographic, and CMR information at the time of interpretation but also to the nature of the study protocol, ie, inclusion of women with MI and the entry criterion of no obstructive CAD. The cardiologist at the enrolling center reviewed the IVUS studies offline while blinded to all other information. Disagreements were resolved by consensus of 2 cardiologists at the core laboratory.

Cardiac Magnetic Resonance Imaging
Patients underwent CMR within 7 days of angiography. All patients were imaged with a 1.5-T MRI system (Avanto, Siemens, Erlangen, Germany) with a phased-array body coil and standard ECG monitoring. Images were acquired during repeated end-expiratory breath holds. Initial scout images were acquired to identify the cardiac axes. For evaluation of cardiac function, ECG-gated cine images were acquired in standard long- and short-axis planes with a segmented steady-state free-precession sequence. A stack of 10 to 15 short-axis slices was used for full coverage of the LV. T2-weighted inversion recovery or turbo spin-echo images were acquired before contrast administration in standard long- and short-axis planes.

Figure 1. Patient flow and proportion with plaque disruption. IVUS indicates intravascular ultrasound. *All patients initially consented to cardiac magnetic resonance imaging (CMR) but then declined. **Includes 5 patients with STEMI.
Table. Clinical ECG, Angiographic, Intravascular Ultrasound, and Magnetic Resonance Imaging Findings

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n = 50)</th>
<th>Plaque Disruption (n = 16)</th>
<th>No Plaque Disruption (n = 26)</th>
<th>P</th>
<th>LGE (n = 17)</th>
<th>No LGE (n = 23)</th>
<th>P</th>
<th>STE (n = 11)</th>
<th>No STE (n = 39)</th>
<th>P</th>
<th>Abnormal T2 (n = 17)</th>
<th>Normal T2 (n = 15)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (mean ± SD), y</td>
<td>56.9 ± 12.8</td>
<td>60.9 ± 11.4</td>
<td>53.5 ± 13.7</td>
<td>0.70</td>
<td>55.4 ± 14.3</td>
<td>57.3 ± 12.7</td>
<td>0.65</td>
<td>52.5 ± 14.7</td>
<td>58.2 ± 12.0</td>
<td>0.26</td>
<td>59.5 ± 14.1</td>
<td>52.0 ± 12.4</td>
<td>0.12</td>
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<tr>
<td>Troponin, median (IQR), ng/mL</td>
<td>1.60 (0.44–4.31)</td>
<td>1.49 (0.53–2.71)</td>
<td>0.96 (0.14–4.13)</td>
<td>0.75</td>
<td>3.13 (1.30–4.03)</td>
<td>1.10 (0.37–1.98)</td>
<td>0.01</td>
<td>1.40 (2.20–4.55)</td>
<td>1.32 (0.16–4.33)</td>
<td>0.32</td>
<td>5.97 (1.96–1.98)</td>
<td>0.86 (0.16–1.30)</td>
<td>&lt;0.001</td>
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<td>Abnormal T2, n (%)</td>
<td>30 (60)</td>
<td>8 (50)</td>
<td>17 (65)</td>
<td>0.35</td>
<td>15 (88)</td>
<td>16 (59)</td>
<td>0.05</td>
<td>8 (73)</td>
<td>22 (56)</td>
<td>0.47</td>
<td>12 (71)</td>
<td>12 (80)</td>
<td>0.61</td>
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<td>DM, n (%)</td>
<td>16 (32)</td>
<td>7 (44)</td>
<td>8 (31)</td>
<td>0.35</td>
<td>6 (35)</td>
<td>8 (30)</td>
<td>0.75</td>
<td>3 (27)</td>
<td>14 (38)</td>
<td>0.17</td>
<td>6 (35)</td>
<td>6 (40)</td>
<td>0.99</td>
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<tr>
<td>Prior MI, n (%)</td>
<td>6 (12)</td>
<td>1 (6)</td>
<td>4 (15)</td>
<td>0.99</td>
<td>2 (12)</td>
<td>4 (15)</td>
<td>0.73</td>
<td>2 (10)</td>
<td>4 (10)</td>
<td>0.85</td>
<td>3 (18)</td>
<td>2 (13)</td>
<td>0.99</td>
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<td>Smoking, n (%)</td>
<td>9 (18)</td>
<td>3 (19)</td>
<td>7 (27)</td>
<td>0.54</td>
<td>4 (24)</td>
<td>4 (15)</td>
<td>0.69</td>
<td>2 (10)</td>
<td>8 (21)</td>
<td>0.80</td>
<td>3 (18)</td>
<td>2 (13)</td>
<td>0.99</td>
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<td>BMI (median, IQR), kg/m²</td>
<td>26.2 (24.4–28.4)</td>
<td>27.6 (24.3–33.7)</td>
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<td>27.4 (24.1–27.3)</td>
<td>26.4 (24.4–30.7)</td>
<td>0.78</td>
<td>25.1 (23.1–27.3)</td>
<td>27.0 (24.4–31.4)</td>
<td>0.11</td>
<td>27.1 (24.8–28.1)</td>
<td>31.4 (25.4–36.3)</td>
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<td>ECG findings, n (%)</td>
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<td>ST-segment elevation</td>
<td>11 (22)</td>
<td>2 (13)</td>
<td>4 (15)</td>
<td>0.47</td>
<td>11 (100)</td>
<td>0 (0)</td>
<td></td>
<td>4 (24)</td>
<td>3 (20)</td>
<td>0.99</td>
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<td>ST-segment depression</td>
<td>7 (14)</td>
<td>2 (13)</td>
<td>2 (8)</td>
<td>0.63</td>
<td>6 (35)</td>
<td>3 (11)</td>
<td>0.23</td>
<td>0 (0)</td>
<td>4 (11)</td>
<td>0.56</td>
<td>1 (6)</td>
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<td>T-wave inversion</td>
<td>22 (44)</td>
<td>10 (63)</td>
<td>10 (38)</td>
<td>0.19</td>
<td>7 (41)</td>
<td>14 (52)</td>
<td>0.36</td>
<td>5 (45)</td>
<td>17 (44)</td>
<td>0.42</td>
<td>9 (53)</td>
<td>4 (27)</td>
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<tr>
<td>Any abnormal segment, n (%)</td>
<td>26 (52)</td>
<td>7 (44)</td>
<td>14 (54)</td>
<td>0.79</td>
<td>6 (35)</td>
<td>7 (26)</td>
<td>0.05</td>
<td>4 (29)</td>
<td>20 (52)</td>
<td>0.51</td>
<td>13 (77)</td>
<td>5 (33)</td>
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<td>LVEF, median (IQR), %</td>
<td>60 (43–63)</td>
<td>56 (49–62)</td>
<td>60 (55–62)</td>
<td>0.66</td>
<td>55 (42–60)</td>
<td>60 (48–65)</td>
<td>0.57</td>
<td>55 (38–60)</td>
<td>60 (48–64)</td>
<td>0.17</td>
<td>55 (45–60)</td>
<td>64 (55–68)</td>
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<td>Best angiographic stenosis, median (IQR), %</td>
<td>15 (30)</td>
<td>0 (0)</td>
<td>13 (50)</td>
<td>0.28</td>
<td>6 (18)</td>
<td>6 (22)</td>
<td>0.73</td>
<td>7 (41)</td>
<td>11 (73)</td>
<td>0.09</td>
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<td>Absence of atherosclerosis, n (%)</td>
<td>15 (30)</td>
<td>0 (0)</td>
<td>13 (50)</td>
<td>0.16</td>
<td>15 (0–30)</td>
<td>30 (0–40)</td>
<td>0.47</td>
<td>30 (15–40)</td>
<td>10 (0–30)</td>
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<td>IVUS findings</td>
<td>n = 42</td>
<td>n = 16</td>
<td>n = 26</td>
<td>n = 42</td>
<td>n = 12</td>
<td>n = 24</td>
<td>n = 6</td>
<td>n = 36</td>
<td>n = 42</td>
<td>n = 13</td>
<td>n = 12</td>
<td>n = 25</td>
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<td>Plaque disruption, n (%)</td>
<td>16 (38)</td>
<td>1 (6)</td>
<td>13 (48)</td>
<td>0.003</td>
<td>2 (33)</td>
<td>12 (33)</td>
<td>0.13</td>
<td>6 (43)</td>
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<td>n = 14</td>
<td>n = 22</td>
<td>n = 17</td>
<td>n = 27</td>
<td>n = 10</td>
<td>n = 34</td>
<td>n = 17</td>
<td>n = 15</td>
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<td>LGE (any), n (%)</td>
<td>17 (39)</td>
<td>1 (7)</td>
<td>11 (50)</td>
<td>0.03</td>
<td>17 (39)</td>
<td>27 (61)</td>
<td>0.35</td>
<td>7 (47)</td>
<td>15 (43)</td>
<td>0.80</td>
<td>8 (47)</td>
<td>4 (27)</td>
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<td>LGE type, n (%)</td>
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<td>Transmural</td>
<td>9</td>
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<td>6</td>
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<td>9</td>
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<td>5</td>
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<td>3</td>
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<td>1</td>
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<td>0</td>
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<td>1.0</td>
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<td>1</td>
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<td>Centromyocardial</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0.67</td>
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<td>0</td>
<td>2</td>
<td>1.0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Subepicardial</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.0</td>
<td>1</td>
<td>0</td>
<td>0.99</td>
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<tr>
<td>Mixed pattern</td>
<td>4</td>
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<td>2</td>
<td>0.70</td>
<td>4</td>
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<td>3</td>
<td>0.99</td>
<td>2</td>
<td>0</td>
<td>0.49</td>
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(Continued)
T2-weighted imaging was incorporated into the protocol after enrollment of 12 patients. Delayed contrast-enhanced T1-weighted images were obtained \( \sim \) 10 minutes after a total dose of 0.15 mmol/kg gadolinium-DTPA with a magnetization-prepared spoiled gradient-echo sequence with the inversion time set to null normal myocardial signal intensity.\(^{13}\) Blood pressure and pulse oximetry were monitored.

### Image Analysis

All images were reviewed by 2 experienced CMR readers (M.B.S., L.A.) who were blinded to ECG, laboratory, angiographic, and IVUS results at the time of interpretation. Any disagreements were resolved by consensus.

The LV was divided according to the American Heart Association 17-segment model for all analyses. T2-weighted images were evaluated on a segmental basis for the presence of increased signal. The presence and pattern of late gadolinium enhancement (LGE) were evaluated for each segment and classified as subendocardial, subepicardial, midwall, or transmural in distribution. Segments with \( >75\% \) LGE based in the subendocardium were classified as transmural. Determination of LGE is highly reproducible.\(^{14}\)

### Statistical Analysis

Descriptive analysis techniques were used to characterize study participants. Center and variability of continuous measures are presented as means and SDs when they followed a normal distribution and as medians and interquartile range otherwise. We compared baseline characteristics and clinical outcomes of the group with plaque disruption and with no plaque disruption, LGE versus none, abnormal T2 versus normal T2, and ST-segment elevation versus no ST-segment elevation. Statistical testing was performed with 2-sample \( t \) tests and nonparametric Wilcoxon rank-sum tests for continuous variables, depending on whether their distribution was gaussian, and the Fisher exact test for categorical variables.

### Results

#### Patients and Testing

A total of 121 women who met clinical inclusion criteria, including no known obstructive CAD, provided informed consent between June 2007 and August 2010; 71 were ineligible because of \( \geq 50\% \) stenosis (n=69), coronary dissection (n=1), or excessive tortuosity (n=1). Fifty women were fully eligible with \(<50\% \) angiographic stenosis of all major vessels. We have previously demonstrated that 32% of women undergoing angiography for MI in our laboratory have \(<50\% \) stenosis; this consecutive sample included women with previously known obstructive CAD.\(^3\) Eight of the 50 patients in the present study did not undergo IVUS for logistical reasons (see Figure 1). Forty-four patients underwent CMR, including 36 of the 42 patients who underwent IVUS; the remaining 6 patients declined CMR after initial consent.

#### Patient Characteristics

Mean age was 57±13 years; 46 of 50 (92\%) presented with chest pain (Table). Six (12\%) had a history of prior MI. Median peak troponin was 1.60 ng/mL (interquartile range [IQR], 0.44–4.31); 88\% of patients had peak troponin \( >5 \) times the upper limit of normal (0.04 ng/mL). Thirty-four patients (68\%) had an abnormal ECG, including ST-segment elevation in 11 patients (22\%), ST-segment depression in 7 (14\%), left bundle-branch block in 1 (2\%), and T-wave inversion (\( \geq 2 \) contiguous leads) in 22 (44\%). Most patients (84\%) were in Killip class I; 3 (6\%) presented with or

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<tr>
<td><strong>PLaque</strong></td>
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<tr>
<td>Abnormal/H11005</td>
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<td>Patients (n=8)</td>
</tr>
<tr>
<td>6 (69)</td>
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<td>2 (25)</td>
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<td>3 (68)</td>
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<td>7 (41)</td>
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<td>20 (100)</td>
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Figure 2. Representative angiographic and intravascular ultrasound (IVUS) images in patients with plaque disruption. The site of plaque rupture or ulceration is marked with an arrow on each angiogram. The artery with the abnormality is indicated for each patient. The right side for each IVUS image shows the outline of the luminal border (yellow) and external elastic lamina (red) corresponding to each IVUS image directly to its left. LAD indicates left anterior descending artery; LCX, left circumflex artery.
developed cardiogenic shock during the admission; 5 (10%) were in Killip class II. Average LV ejection fraction was 55%±14%; LV ejection fraction was ≤40% in 10 patients (20%). A suspected culprit vessel could be identified on the basis of the ECG, wall motion abnormalities, or angiography in 23 of 50 patients (46%).

**Angiographic Findings**
Fifteen patients (30%) had completely normal coronary angiography. The remaining patients had some degree of coronary stenosis, ranging from mild luminal irregularities to 45% diameter stenosis. The median worst diameter stenosis by visual estimation on angiography was 20%. Myocardial bridging was observed in the LAD of 2 patients.

**Intravascular Ultrasound Findings**
Sixteen of 42 patients (38%) undergoing IVUS at median of 2 days (IQR, 1–2 days) after the onset of ischemic symptoms had plaque disruption. Twelve patients (29%) had plaque rupture, including 2 patients with multiple plaque ruptures and 1 patient with plaque rupture and a distinct plaque ulceration (Figure 2). Four additional patients had plaque ulceration only (10%). The plaque rupture was located in the LAD in 7 patients (58%), the left circumflex artery in 3 (25%), and both the LAD and left circumflex in 2 (17%). The right coronary artery was imaged in 5 of 42 patients. Plaque ulceration was located in the LAD in 3 patients and the left circumflex artery in 2 patients. Evaluation for plaque disruption (rupture or ulceration) was concordant in 92% of vessels; the remaining vessels were resolved by consensus. Patients with plaque disruption had higher maximal angiographic diameter stenosis (median worst diameter stenosis, 40% [IQR, 30%–45%] versus 0% [IQR, 0%–20%] without plaque disruption; \( P < 0.001 \)). Plaque rupture was identified in normal-appearing segments (Figure 2), but not in patients with com-

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**Figure 3.** Representative cardiac magnetic resonance images showing late gadolinium enhancement (LGE; left) with corresponding end-diastolic cine image (right). **A**, Small, nearly transmural LGE involving the mid inferior wall (arrow). **B**, Patchy areas of LGE throughout the left ventricle that are primarily midwall, with some septal areas extending to the right ventricular subendocardium (white arrows) and a nearly transmural area in the apical lateral wall (black arrow). **C**, Representative images showing a mixed pattern of LGE: multiple separate areas of enhancement demonstrating midwall (white arrow) and transmural (black arrows) involvement.
pletely normal angiograms, ie, without luminal irregularities. There was no relationship between plaque disruption and the presence of LV wall motion abnormalities or ECG changes (Table). Peak troponin was similar among those with and without plaque disruption (median peak troponin, 1.49 ng/mL versus 0.96 ng/mL, respectively; P = 0.75). One patient had a non-flow-limiting distal coronary dissection resulting from guidewire manipulation during IVUS that had no adverse consequences; the patient declined CMR.

**Cardiac Magnetic Resonance Findings**

Among 44 patients who underwent CMR at a median of 6 days (IQR, 4–8 days) after symptom onset, 17 (39%) had at least 1 area of LGE. Evaluation for LGE was concordant for 96% of segments; the remaining segments were resolved by consensus. Late gadolinium enhancement was associated with higher peak troponin (median, 3.13 versus 1.10 ng/mL; P = 0.01) and abnormal LV wall motion (59% versus 26%; P = 0.05; Table). Ten of the 17 patients with LGE had a transmural or subendocardial pattern typical of an ischemic injury (59%); 3 had a subepicardial or midwall pattern typical of a nonischemic insult (18%); and 4 had both an area of transmural LGE and a distinct area of midwall LGE (mixed pattern, 24%; Figure 3). Patients with ST-segment elevation more likely to have an ischemic LGE pattern. A likely culprit vessel could be identified from the ECG, wall motion, and/or angiography in 9 of 17 patients with LGE. The region of LGE corresponded to the territory of the suspected culprit in 8 of these 9 patients (89%). The median number of segments with LGE was 2 (IQR 1–3); however, often only part of a segment was involved (Figures 3 and 4).

Among 32 patients who underwent T2-weighted imaging, 17 (53%) had abnormal T2 signal in at least 1 area. This included 9 patients without LGE and 8 patients with LGE (4 transmural, 2 midwall or subepicardial, 2 mixed pattern). Evaluation for abnormal T2 was concordant for 93% of segments; the remaining segments were resolved by consensus. Patients with abnormal T2 signal had higher peak troponin (median, 5.97 versus 0.66 ng/mL; P < 0.001) and were more likely to have abnormal LV wall motion (77% versus 33%; P = 0.03). Time from MI to CMR was not different between those patients with and those without T2 signal hyperintensity. A likely culprit vessel could be identified in 10 of 17 patients with abnormal T2 signal. In each of these patients, the region of abnormal T2 signal corresponded to the territory of the suspected culprit. The median number of segments with T2 hyperintensity was 4 (IQR, 3 to 7).

**Correlation of Magnetic Resonance Imaging and Intravascular Ultrasound Findings**

Figure 4 shows angiographic, IVUS, and CMR images from representative cases with different constellations of findings. Among 16 patients with plaque disruption on IVUS, 14 underwent CMR. Only 1 patient with plaque disruption had LGE, in an ischemic pattern. T2 hyperintensity was noted in 6 of 8 patients with plaque disruption in whom T2-weighted imaging was performed. The remaining patients with plaque disruption were enrolled before T2-weighted imaging was included in the study CMR protocol. Among 26 patients without plaque disruption, 22 underwent CMR and 11 of 22 had LGE (P = 0.03 vs patients with plaque disruption).

**Patients With Takotsubo Cardiomyopathy**

Four patients (8%) met the criteria for takotsubo cardiomyopathy. One had 45% right coronary artery stenosis and an angiographically normal LAD; 1 had 45% LAD stenosis; and the other 2 had no angiographic stenoses. Two patients with takotsubo cardiomyopathy had plaque ulceration on IVUS, 1 in the LAD (Figure 5) and 1 in the left main. The other 2 patients had no atherosclerosis on angiography or IVUS. Three of the 4 patients with takotsubo cardiomyopathy underwent CMR; none had LGE. Two patients (1 with plaque ulceration) who underwent T2-weighted imaging had signal hyperintensity in all mid and apical segments, a pattern now considered typical of takotsubo cardiomyopathy.15

**Discussion**

In this study, the first prospective evaluation using IVUS and CMR in women presenting with acute MI without obstructive CAD at angiography, we have demonstrated that plaque disruption is a frequent finding. We have also shown that LGE commonly identifies the location and pattern of myocardial damage and that T2 signal hyperintensity is frequently present, indicating acute myocardial edema. T2 signal hyperintensity was particularly common among women with plaque disruption, but LGE was infrequent with plaque disruption. In this cohort, IVUS and CMR provided complementary information and together revealed abnormalities in 35 of 50 patients (70%).

Plaque rupture or ulceration was identified by the blinded core laboratory in 38% of women undergoing IVUS in this study. Plaque disruption often occurred in segments that were

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**Figure 4 (Continued).** Colocalization of angiographic, intravascular ultrasound (IVUS) and cardiac magnetic resonance (CMR) images in patients with different constellations of findings. The site of IVUS imaging is marked on each angiogram. A. Plaque rupture with increased T2 signal and absent late gadolinium enhancement (LGE). Left coronary angiogram (i) with corresponding IVUS showing plaque rupture in the mid left anterior descending artery (LAD; ii and iii). T2 signal hyperintensity is noted to involve the mid anterior and mid and apical anterior septal walls (iv and v). No LGE is noted within the myocardium in 2 planes (vi and vii). Normal left ventricular (LV) function (viii and ix). B. Plaque rupture with LGE. Angiogram of the left coronary artery (i) with corresponding IVUS showing plaque rupture in the proximal LAD (ii and iii). The site of the IVUS images is marked with an arrow. Subendocardial to transmural LGE involving the basal anteroseptal wall in shown in the 3-chamber and short-axis views (iv and v). T2-weighted imaging was not performed in this patient. Normal LV function (vi and vii). C. Ischemic-type LGE without plaque rupture on IVUS. Left coronary angiogram (i). An IVUS of the left circumflex artery (LCx) showing mixed fibrofatty plaque without rupture (ii and iii). The LAD and LCx were imaged with IVUS in this case. T2 signal hyperintensity of the mid inferior, mid inferoseptal, and adjacent right ventricular walls near the right ventricular insertion (iv). Transmural LGE involving subsegments of the same region (v). Normal LV function (vi and vii). D. Nonischemic-type LGE with minimal atherosclerosis on IVUS. Left coronary angiogram (i). Normal IVUS of the LCx (ii and iii). T2 signal hyperintensity of the basal inferior/inferolateral wall (iv). Focal area of midmyocardial LGE involving the same region (v). Normal LV function (vi and vii).
angiographically normal but was not seen in patients with completely normal coronary angiograms, ie, without luminal irregularities. The finding of plaque disruption in angiographically normal segments is consistent with prior reports in vivo using IVUS or during pathological examination. Atherosclerotic plaques that are destined to cause late events have more severe plaque burden on IVUS than is usually appreciated on angiography. No clinical or ECG variables were associated with plaque disruption. The study population was similar in terms of age and proportion with ST-segment elevation to women with MI seen in our laboratories. As has been described in patients with obstructive CAD and MI, we found that some patients had multiple plaque ruptures or rupture in 1 location and ulceration in another.

We have confirmed a long-held hypothesis about the cause of MI with no obstructive CAD. There is every reason to believe that plaque ruptures in these women were etiologic for MI. Plaque disruption was accompanied by CMR evidence of myocardial edema in the majority of cases, and all patients had acute presentation with chest pain. The entry criteria for this study were created to select patients with acute MI who were referred for coronary angiography on clinical grounds. Plaque rupture is also known to occur in patients with stable angina, and not all plaque rupture events are symptomatic. We did not include stable patients with nonobstructive CAD in this study as control subjects. However, a recent report of 100 women undergoing IVUS with stable chest pain and normal coronary angiography did not identify plaque rupture or ulceration in any patient. Another series using IVUS in 55 patients with chest pain and normal coronary angiography also did not identify plaque rupture. Therefore, it appears likely that plaque rupture is related to the acuity of the presentation and the degree of angiographic stenosis in stable patients. We hypothesize that plaque disruption as observed in this study was accompanied by distal embolization of atherothrombotic debris or platelet aggregates or by transient or incomplete thrombosis with endogenous thrombolysis, leading to widely patent arteries by the time of angiography a median of 2 days after symptom onset.

Myocardial injury, confirmed in all patients by troponin elevation, was commonly observed on imaging studies, as evidenced by T2 signal hyperintensity in 53% of the patients tested. In only 1 case in this series was LGE associated with plaque disruption, but T2 hyperintensity was common in patients with plaque disruption, seen in 75% of the patients examined. Myocardial edema is a known early consequence of ischemia. It is possible that earlier CMR would have shown LGE or T2 abnormalities in a greater proportion of patients, but we believe this is unlikely on the basis of prior studies suggesting persistence of these abnormal findings, usually up to at least 2 weeks. Plaque disruption was not associated with evidence of more severe myocardial injury based on peak troponin or LGE. This suggests that endogenous thrombolysis and/or relief of superimposed vasospasm may have occurred before more extensive and irreversible myocardial injury was sustained and that troponin elevation in these patients represents death of smaller groups of myocytes distributed throughout the territory at risk. The territory at risk was large in many cases, as can be appreciated from the representative angiograms and T2-weighted images. If hypoperfusion related to the culprit vessel had lasted for a longer period of time and resulted in more necrosis, the vessel might have been expected to display significant stenosis at angiography and therefore the patient would have been excluded from this study. Of note, no patient with plaque disruption had a pattern that would suggest a nonischemic mechanism such as myocarditis.

The finding of plaque disruption in a patient with MI and nonobstructive CAD has implications for treatment. Such patients would presumably benefit from treatment with antiplatelet agents and statins. However, patients without obstructive CAD are less likely to be prescribed medical therapies for secondary prevention of MI, including aspirin, clopidogrel, and statins. Patients with MI and no obstructive CAD have an ≈2% risk of death or reinfarction over 6 to 12 years. However, most of these patients would presumably benefit from treatment with antiplatelet agents and statins. The finding of plaque disruption in a patient with MI and nonobstructive CAD has implications for treatment. Such patients would presumably benefit from treatment with antiplatelet agents and statins. However, patients without obstructive CAD are less likely to be prescribed medical therapies for secondary prevention of MI, including aspirin, clopidogrel, and statins. Patients with MI and no obstructive CAD have an ≈2% risk of death or reinfarction over 6 to 12 years. However, most of these patients would presumably benefit from treatment with antiplatelet agents and statins.
months\textsuperscript{25,26} and a $>15\%$ readmission rate within 6 months.\textsuperscript{27} It is possible that women with disrupted plaque are at highest risk for events among those with MI and nonobstructive CAD, particularly if they are not provided appropriate secondary prevention measures. This hypothesis remains speculative, but the use of IVUS during angiography in patients with MI and no obstructive CAD with follow-up for outcomes would help to confirm it.

The most common LGE pattern was ischemic (transmural or subendocardial). Ischemic-type LGE without obstructive CAD has also been observed in heart failure patients.\textsuperscript{28,29} Nearly one third of patients with an ischemic LGE pattern had angiographically normal coronary arteries, but all had some atherosclerosis on IVUS. Only 1 patient had plaque rupture. Review of LGE images shows that MIs in this study were generally small infarctions, which may be surmised from the median peak troponin of 3.1 ng/mL. We hypothesize that vasospasm of, embolism to, or perhaps flush occlusion of a branch vessel was the cause of MI in these patients. The appearance of ischemic LGE in these patients is remarkably similar to that reported in a study examining embolic phenomena around the time of percutaneous coronary intervention, ie, subendocardial-to-transmural LGE involving a small portion of the myocardial segment affected.\textsuperscript{30} Embolism in our cases could have originated from a proximal plaque disruption or a noncoronary source. A nonischemic cause such as sarcoidosis or myocarditis is also possible with an ischemic-type LGE pattern. Women are much more likely than men to develop cardiac syndrome X, the stable ischemic syndrome resulting from endothelial and/or microvascular dysfunction without angiographically obstructive CAD. Vasospasm causing MI may represent an extreme form of endothelial dysfunction, perhaps linking the predominance of female patients in cardiac syndrome X and MI with no obstructive CAD.

The frequency of abnormal LGE in our cohort was similar to that reported in prior series of patients with chest pain, troponin elevation, and no obstructive CAD.\textsuperscript{31–35} The distribution of patterns was different than in prior studies,\textsuperscript{32,33} likely related to demographic and clinical characteristics. For example, studies reporting a higher frequency of nonischemic LGE (eg, myocarditis) included younger, predominantly male cohorts,\textsuperscript{31,33,34} often with a requirement for completely normal angiography, as opposed to the present series of women with a clinical diagnosis of MI. Some prior reports specifically excluded patients with a clinical diagnosis of MI. The 1 study that included a predominantly female patient population found a higher rate of ischemic-type LGE, as did our study.\textsuperscript{35}

Four patients in this study had LGE patterns that were not typical of ischemic or nonischemic disease. Such mixed patterns have also been described in patients with heart failure undergoing CMR for etiologic diagnosis.\textsuperscript{28} The appearance of scans in individual patients may suggest a higher likelihood of ischemic or nonischemic disease or a combination.

We identified plaque ulceration in 2 patients who met the criteria for takotsubo cardiomyopathy, 1 patient with ulceration in the left main coronary artery and 1 patient with ulceration in the LAD. Each of these patients had a large LAD that wrapped around the apex and could potentially account for a large area of wall motion abnormality. Plaque rupture has previously been reported in patients with takotsubo cardiomyopathy\textsuperscript{36,37} but was not identified in a recent IVUS series.\textsuperscript{38} Most authors hypothesize that takotsubo cardiomyopathy is due to catecholamine toxicity, autonomic dysfunction, and/or multivessel coronary spasm.\textsuperscript{3} However, the takotsubo LV dysfunction pattern occurs in anterior MI.\textsuperscript{39} Our findings support the concept that takotsubo cardiomyopathy may have several pathophysiological mechanisms, including plaque disruption in the LAD or left main artery.

**Limitations**

The present study was a small, single-center study limited to women. Men were not included because the prevalence of nonobstructive CAD is higher in women and because mechanisms may differ by sex. We therefore chose to focus on the larger population of women to allow an adequate sample size, avoiding inclusion of a small number of men that might dilute the overall findings observed. We were not able to perform IVUS or CMR in all patients owing to logistical problems and withdrawals of consent. Ideally, IVUS of all 3 coronary arteries would have been performed in all patients, and this could have resulted in a higher proportion of patients with plaque disruption or multiple plaque disruption, particularly considering the low rate of imaging of the right coronary artery. Quantitative coronary angiography and virtual histology IVUS were not performed. Study enrollment started during a time when the importance of T2-weighted imaging in cardiac MR was just being realized; shortly thereafter, an optimized, robust T2-weighted technique was available and was incorporated into the CMR protocol. There was no control group within this study for comparison of plaque disruption frequency; the most scientifically appealing control group would have been stable women without obstructive CAD, who were not included because of potential risks of IVUS. Nonetheless, this is the largest prospective series of women with MI and no obstructive CAD in which CMR and IVUS data were gathered prospectively and interpreted by experienced observers in experienced laboratories by investigators who were blinded to clinical data. Thus, we are able to offer important insights into the mechanisms of MI with nonobstructive CAD.

**Conclusions**

Plaque rupture and ulceration are common findings in women with MI and nonobstructive CAD on angiography. This proves a long-held hypothesis regarding the mechanism of MI with nonobstructive CAD. From our results, it is apparent that there is more than 1 clinical syndrome of MI with no obstructive CAD at angiography, with causes including occult plaque disruption, ischemic injury without plaque disruption, inflammatory or infiltrative etiologies, takotsubo cardiomyopathy, and possibly others that were not identified using the combination of IVUS and CMR. Intravascular ultrasound and CMR provide distinct, complementary information in patients with MI and no obstructive CAD and could be considered for use in series to permit categorization of potential mechanisms in these patients. Such classification will facilitate future research into the mechanisms and treatment of MI with nonobstructive CAD.
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Disclosures
None.

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**CLINICAL PERSPECTIVE**

There is no angiographically demonstrable obstructive coronary artery disease in a substantial proportion of patients with myocardial infarction, particularly women. Plaque rupture has long been hypothesized to be a cause of myocardial infarction with nonobstructive coronary artery disease. We sought to determine the mechanism(s) of myocardial infarction in this setting using intravascular ultrasound during angiography and cardiac magnetic resonance imaging performed within 1 week. Fifty women were enrolled with median worst coronary angiographic stenosis of 20% and median peak troponin of 1.60 ng/mL. Plaque disruption (rupture and/or ulceration) was found on blinded core laboratory intravascular ultrasound review in 38% of patients tested. Late gadolinium enhancement (LGE) was identified in 39% and abnormal T2 signal in 53% of women undergoing cardiac magnetic resonance imaging. The most common LGE pattern was ischemic (transmural/subendocardial). Nonischemic (midmyocardial/subepicardial) and mixed LGE patterns were also observed. T2 signal hyperintensity was common and LGE was infrequent among patients with plaque disruption. We hypothesize that vasospasm of, embolism to, or flush occlusion of a branch vessel caused myocardial infarction in patients with an ischemic LGE pattern but without plaque disruption. Intravascular ultrasound and cardiac magnetic resonance imaging provided complementary information in this cohort and together revealed abnormalities in 35 of 50 patients (70%). In this study, the first prospective evaluation using intravascular ultrasound and cardiac magnetic resonance imaging in women with acute myocardial infarction and without obstructive coronary artery disease at angiography, we have demonstrated that plaque disruption is a frequent finding. We have also shown that LGE commonly identifies the location and pattern of myocardial damage and that acute myocardial edema is frequently present in these patients.

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Mechanisms of Myocardial Infarction in Women Without Angiographically Obstructive Coronary Artery Disease

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