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What Causes Myocardial Infarction in Women Without Obstructive Coronary Artery Disease?

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Women experience higher mortality rates and more adverse outcomes after acute myocardial infarction (AMI) than men, despite less obstructive coronary artery disease (CAD) and plaque burden with similar plaque responses to intensive risk factor modification.¹ Furthermore, nonobstructive CAD by angiography appears to be emerging as a predictor of mortality in women, but not among men.² These puzzling findings illustrate our incomplete understanding of sex-specific differences in pathophysiological mechanisms of AMI and ischemic heart disease in general. A better understanding of the mechanisms would lead the way for improvement in attempts to optimize ischemic heart disease management among women.

In the current issue, Reynolds and colleagues³ provide new data to help advance our understanding in this area by using intravascular ultrasound (IVUS) and cardiac magnetic resonance imaging (CMR) to investigate women with AMI in the absence of obstructive CAD. They provide the first evidence for plaque disruption and myocardial tissue characteristics among women with confirmed AMI and normal or only minimally abnormal coronary angiograms. To help interpret their novel findings, it seems appropriate to briefly review what we know in this area.

Although sex-related results were lacking, autopsy studies from past decades securely linked severe atherosclerotic CAD and intracoronary thrombosis with AMI leading to death. More recent and detailed studies of women and men dying with AMI added disrupted plaque as the culprit for the acute thrombotic event. Overall, the majority had plaque rupture; a third had erosion; and a few percent had calcified nodules contributing to the thrombi.⁴ Interestingly, plaque erosion was identified as the cause of death in about one third of women, whereas in men, erosion was only about half as frequent as the cause of death. More important, erosion was observed as the cause of acute coronary thrombi in the majority of women <50 years of age who died suddenly. Thus, the substrate for coronary thrombus leading to AMI and death appears to be both sex and age dependent. Plaque rupture is the predominant mechanism for disruption in women >50 years of age and in men regardless of age, whereas erosion is the predominant mechanism in younger women.⁴

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None.

Because autopsy studies are limited in their ability to identify precursor substrates for these acute events, attention turned to the cardiac catheterization laboratory. Many older and very well-conducted prospective angiographic studies (eg, from the Coronary Artery Surgery Study [CASS] Registry,⁵) securely linked increasing stenosis and extent of CAD with progressively increasing risk for AMI and death. However, no helpful sex-specific information was provided, in part because 85% to 90% of the cases studied were men. Nevertheless, these reports confirmed and extended the autopsy conclusions from fatal cases to nonfatal cases: The substrate for AMI is severe coronary atherosclerosis. This conclusion appeared to be challenged by retrospective reports suggesting that minimal lesions on angiography may be precursor lesions for plaque disruption leading to acute coronary syndrome (ACS). Indeed, our overview of angiographic results from many ACS studies found that 20% to 30% of women presenting with biomarker-positive ACS had no obstructive CAD.⁶ Such angiographic findings were only half as frequent among men. On first look, these findings may seem at variance with the conclusions from autopsy and older prospective angiographic studies of severe CAD among fatal and nonfatal ACS. However, there would likely be many more minimal lesions than severe lesions, so even if risk for plaque disruption were similar between these lesions, the likelihood for a patient to have a minimal lesion associated with the AMI would always be greater.

Then IVUS studies documented that culprit lesions associated with ACS tend to have severe coronary atherosclerosis (eg, larger plaque burdens [\approx 60% to 80%], remodeling indexes, and thrombus volumes).⁷ Additionally, severe atherosclerosis usually underlies angiographic minimal lesions, and this severe disease is often obscured by remodeling. So, the process of compensatory enlargement of the vessel to maintain coronary artery lumen size was rediscovered.⁸ These IVUS studies also suggested that plaque rupture per se did not necessarily result in symptoms or death, but that the presence of rupture, with a smaller lumen size, and/or thrombus usually provides the substrate for the clinical expression of ACS.⁷

In addition, questions were raised about whether ACS, among patients with no obstructive disease by angiography, could be related to plaque disruption or perhaps acute coronary occlusion by other mechanisms (eg, spasm, enhanced coagulation, impaired fibrinolysis, microvascular disease, etc.). Some reports have linked female-unique disorders (polycystic ovarian syndrome, hypothalamic hypoenestrogenemia, etc) and other conditions highly prevalent among women (lupus, rheumatoid arthritis, giant-cell arteritis, etc). Several recent reports have identified provoked coronary artery spasm in 50% to 70% of ACS patients without obstructive CAD.⁹ Interestingly, despite prior reports among more clinically stable patients showing higher frequencies of coronary spasm in women versus men, these new reports in ACS patients did not link coronary artery spasm with sex.

Within this background, the report by Reynolds and colleagues³ advances our understanding of AMI in women. Several points from their report require emphasis, along with discussion of some limitations. First, and perhaps most important, they have confirmed that evidence for plaque disruption by IVUS was present in almost 40% of women with ACS and nonobstructive CAD. Considering the sampling limitations of IVUS, this likely underestimates the true frequency of plaque disruption among such women. Unfortunately,

they did not provide information to indicate whether spasm testing was performed. From the mechanistic standpoint, this is an important piece of the puzzle, because increased smooth muscle reactivity is highly prevalent in women and men with ACS and nonobstructive CAD, as noted above. It is puzzling that evidence for plaque disruptions by IVUS did not seem to correlate with an ischemic pattern on CMR (only 1 of 14 such women). This was in contrast to the finding that half of the women (11 of 22) without IVUS evidence of plaque disruption showed an ischemic pattern on CMR. Their suggestions about relief of spasm and/or endogenous fibrinolysis are also important areas for future investigations that merge CMR and IVUS details with testing coronary smooth muscle reactivity and coagulability. Spasm could have accounted for an ischemic pattern on CMR, particularly in the absence of plaque rupture. Nevertheless, their observations provide direction for future investigation into the prospective identification of which coronary artery sites, and/or which women, are likely candidates for disruption and which are likely to be linked with acute events. Finding such patients was recently noted as a priority by our National Heart, Lung, and Blood Institute working group on Identifying Patients at High Risk of a Cardiovascular Event in the Near Future.¹⁰

Second, although the authors state that they did not observe evidence for plaque rupture among the women with completely normal coronary angiography, they did not provide information about whether this subsample (15 women) had plaque by IVUS. This is important mechanistically and for providing direction for prevention management. Given our Women's Ischemic Syndrome Evaluation (WISE) IVUS substudy documenting plaque among $\approx 80\%$ of clinically stable women with ischemic heart disease,¹¹ in addition to other IVUS reports¹² among patients with normal coronary angiography, it seems that the overwhelming majority of women (and men) presenting with clinically stable and unstable ischemic syndromes have coronary plaque when they have atherosclerosis risk factors. Thus, it would not be appropriate to simply assume that such patients with so-called normal coronary angiograms have no coronary atherosclerosis, because such an assumption has the potential to result in a lost opportunity for appropriate prevention therapies. In addition, the possibility of microvascular abnormalities should be considered among those women with late gadolinium enhancement on CMR. This deserves additional consideration, because coronary microvascular dysfunction has been linked with adverse outcomes among women with stable ischemic heart disease and nonobstructive CAD.¹³ Microvascular vascular dysfunction would have the potential to amplify the consequences of an upstream spastic or thrombotic event.

Third, Reynolds et al did not present data on vessel remodeling, which is important because positive remodeling leads to underestimation of atherosclerosis severity/burden, as noted above. Furthermore, because wall stress is directly proportional to vessel diameter, positive remodeling would be expected to increase the likelihood of plaque disruption (rupture/erosion). Although the plaque disruptions observed appeared at sites of minimal or no stenosis, IVUS measures of plaque burden, stenosis area, and remodeling indexes could have provided valuable insights.

Fourth, the authors provide interesting new evidence for plaque disruption by IVUS among 2 of the 4 women thought to have stress-related cardiomyopathy. This provides a possible

mechanistic explanation of the findings associated with this intriguing disorder. Again, information on the presence of plaque and plaque burden from the sties with and without plaque disruption would have been helpful.

From the clinical standpoint, it would be highly desirable to be able to identify disruption-prone lesions at risk for thrombosis in the near term.¹⁰ We know that the clinical expression (ranging from asymptomatic plaque to progression with angina to ACS or even to sudden death) likely is also determined by underlying plaque burden, endogenous coagulation and fibrinolytic systems, vascular smooth muscle tone, and numerous other factors, including sex and sex hormone status. Several novel methods have evolved to identify these disruption-prone plaques. Although intravascular catheters are limited by their range of sampling, the close proximity to the coronary artery luminal surface makes these techniques attractive, particularly if the patient is already undergoing invasive coronary angiography. From this perspective, radiofrequency IVUS, optical coherence tomography, and near-infrared spectroscopy combined with IVUS appear very promising. All of these techniques are under investigation relative to their usefulness to predict future plaque-related events, and our hope is that these studies will have adequate statistical power to provide meaningful sex-specific data. As illustrated here, IVUS and CMR are also very valuable diagnostic techniques to detect coronary abnormalities potentially responsible for the ischemic event and to evaluate myocardial injury. The finding of AMI with no angiographic evidence of obstructive CAD likely subtends a variety of pathophysiological mechanisms that require further investigation among both women and men.

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