Not Just a Man's Disease: Rethinking Coronary Artery Disease in Women

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Published online January 23, 2018; Updated June 13, 2021

Coronary artery disease (CAD) is the number one cause of death of women in the United States[1]; in fact, women are five times as likely to die from CAD than from breast cancer.[2] Yet for decades, CAD—a condition in which plaque builds up in the coronary arteries—has been thought of as a "man's disease," a misunderstanding that has had deadly consequences for women. Large-scale studies show that women with CAD are consistently underdiagnosed, undertreated, and more likely to have adverse outcomes compared to men.[2] As cardiovascular medicine makes such great strides in so many areas, it begs the question: What makes treating CAD in women so challenging?

According to Claire Duvernoy, M.D., interventional cardiologist at the University of Michigan, one of the biggest challenges is lack of timely recognition when a woman is having CAD symptoms. "That seems to be the thing that comes out over and over again when you look at data on why there are worse outcomes," she says. "Often both the patients don't recognize what's happening to them, so they don't see the urgency, and the providers that they eventually do present to don't see them as having an acute coronary syndrome in the same way or with the same urgency as they tend to see men. Ultimately, we know that with delay comes worse outcomes." Duvernoy and her University of Michigan colleague, interventional cardiology fellow Emily Perdoncin, M.D., recently coauthored a review on treatment of CAD in women.

"Honestly, treating women is just different than treating men," adds Karla Kurrelmeyer, M.D., cardiologist at Houston Methodist DeBakey Heart & Vascular Center. "They present differently, you use stress tests differently, there are more autoimmune diseases, and more things that can cause the chest pain other than just coronary artery disease that you have to be aware of."

ATYPICAL PRESENTATION AND HIGH RISKS

Although some women present with chest pain, many display a myriad of atypical and sometimes subtle symptoms that can be misleading. Potential red flags include nausea, fatigue, difficulty breathing, or pain in the jaw, back, or neck. Perdoncin cautions physicians that "even if a woman isn't having the classic 'Hollywood heart attack,' any patient with chest pain or atypical symptoms and risk factors should be treated with the same index of suspicion as men with a similar background would be treated. It's important to not dismiss chest pain in women as psychological and anxiety related."

This high rate of atypical symptoms has deadly consequences for young women with diabetes, according to Kurrelmeyer, who recently wrote a review of imaging for CAD in women for the *Methodist DeBakey Cardiovascular Journal*. Indeed, diabetes raises a woman's risk of CAD threefold.[2] Registry data show that young women with diabetes have the highest rates of death among patients with CAD.

"These young women have had diabetes for a long time and present to the hospital with atypical symptoms, and frequently their heart attacks are missed for a day or two," says Kurrelmeyer. "If you miss the diagnosis, time is muscle, so they have permanent damage and just don't do as well as someone who was diagnosed earlier."

Another problem for women is that certain risk factors for CAD carry proportionally greater risk for women than for men. For instance, women who smoke have twice the risk of CAD than male smokers, and diabetes and high triglycerides are stronger risk factors for women. Even family history can be weighted against women: Having female relatives with premature CAD confers a greater risk compared to the same history in male relatives.[2]

DIAGNOSTIC IMAGING

Unfortunately for women, cardiology has been historically unprepared to deal with the different ways that women with CAD respond to traditional testing. For instance, Kurrelmeyer points out, women will increase their heart rate rather than stroke volume, and breast tissue can interfere with some imaging modalities.

"When stress tests were being developed to detect coronary artery disease back in the 1980s, the researchers realized that the atypical results in women were really a problem, so in all those original studies, they just excluded the women and studied the performance of stress testing exclusively in men," Kurrelmeyer explains. "That pushed the field far behind for women, so now we're trying to figure out how to overcome some of these differences so that the testing is just as accurate in women as in men."

The most common stress test for CAD is exercise electrocardiography (ex-ECG), and although it works well for men, it is much less accurate in detecting CAD in women. It has a high rate of false positives and cannot detect nonobstructive disease. Nonobstructive CAD affects the small coronary artery network, or microvasculature, instead of causing blockages in the main coronary arteries (Figure 1) and is far more common in women than in men. Kurrelmeyer is often frustrated by the emphasis on ex-ECG as a first-line test regardless of gender.

"If you look at the European guidelines, they don't even list ex-ECG as a modality to evaluate women for heart disease because they realize that it's not accurate at all in women," she points out. "It's still in our U.S. guidelines and that's very distressing because it's not a very accurate test in women who have an intermediate pretest probability.3 There are so many false positives in women that frequently it doesn't even pay to do the test. But insurance companies insist that we have to do an exercise ECG first because, according to the guidelines, that's the initial test in someone who can exercise and has a normal resting ECG."

An alternative stress test is stress echocardiography (echo) (Figure 2). Stress echo is Kurrelmeyer's "go-to test." It is more accurate than ex-ECG in diagnosing obstructive CAD and stratifying women into low- and high-risk groups and provides valuable information such as left ventricular ejection fraction assessment or whether a patient has other reasons for atypical chest pain such as mitral valve prolapse or pericarditis. Moreover, it does not expose patients to radiation, making it ideal for premenopausal patients. However, stress echo cannot detect nonobstructive CAD and often produces low-quality images in obese patients.

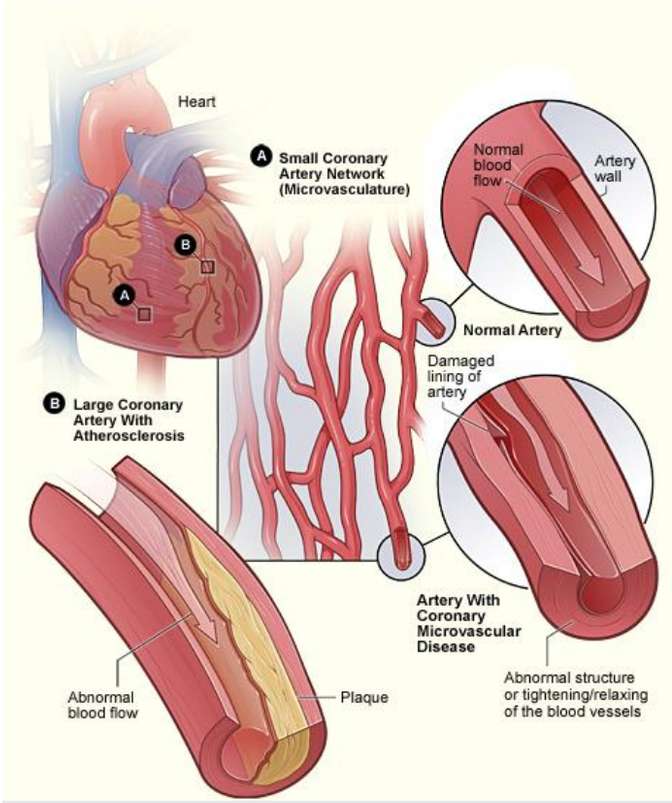

Figure 1.
A shows the small coronary artery network (microvasculature), containing a normal artery and an artery with nonobstructive CAD (microvascular disease). B shows a large coronary artery with plaque buildup. (Source: National Heart, Lung, and Blood Institute)

Of course, no matter how much information a physician can get from a stress test, none of those modalities will detect nonobstructive CAD. Although this condition puts women at risk for myocardial infarction, it has been notoriously difficult to diagnose using the standard stress testing protocols because it does not cause flow-limiting coronary artery lesions.

"In women with nonobstructive CAD, all of the stress tests are going to be negative except for an imaging test like CT angiography. The stress tests just don't pick up subclinical disease," explains Kurrelmeyer.

To accurately diagnose nonobstructive disease, she turns to computed tomography angiography (CTA) (Figure 3). CTA can detect subclinical lesions, calcified and noncalcified plaque, and obstructive and nonobstructive atherosclerosis, and it has comparable sensitivity and specificity in diagnosing CAD in men and women. However, Kurrelmeyer cautions against

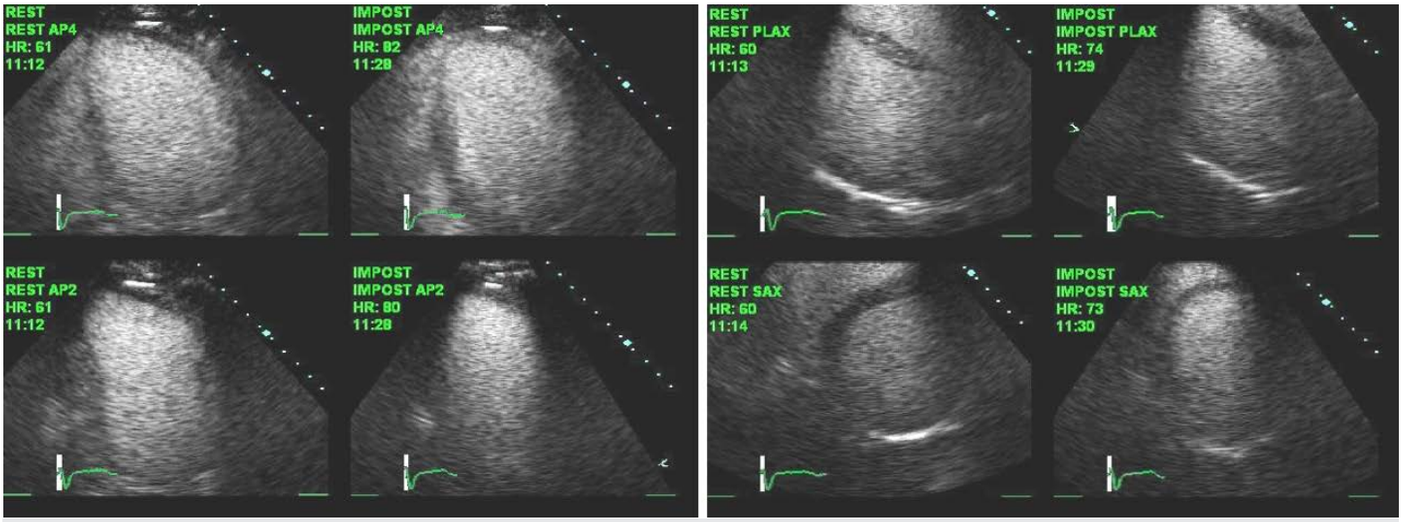

Figure 2.
Treadmill contrast stress echo. Because the apex does not thicken with the rest of the walls post treadmill stress testing (IMPOST), further testing with computed tomography angiography (CTA) or invasive angiography is necessary. Baseline images are labeled REST.

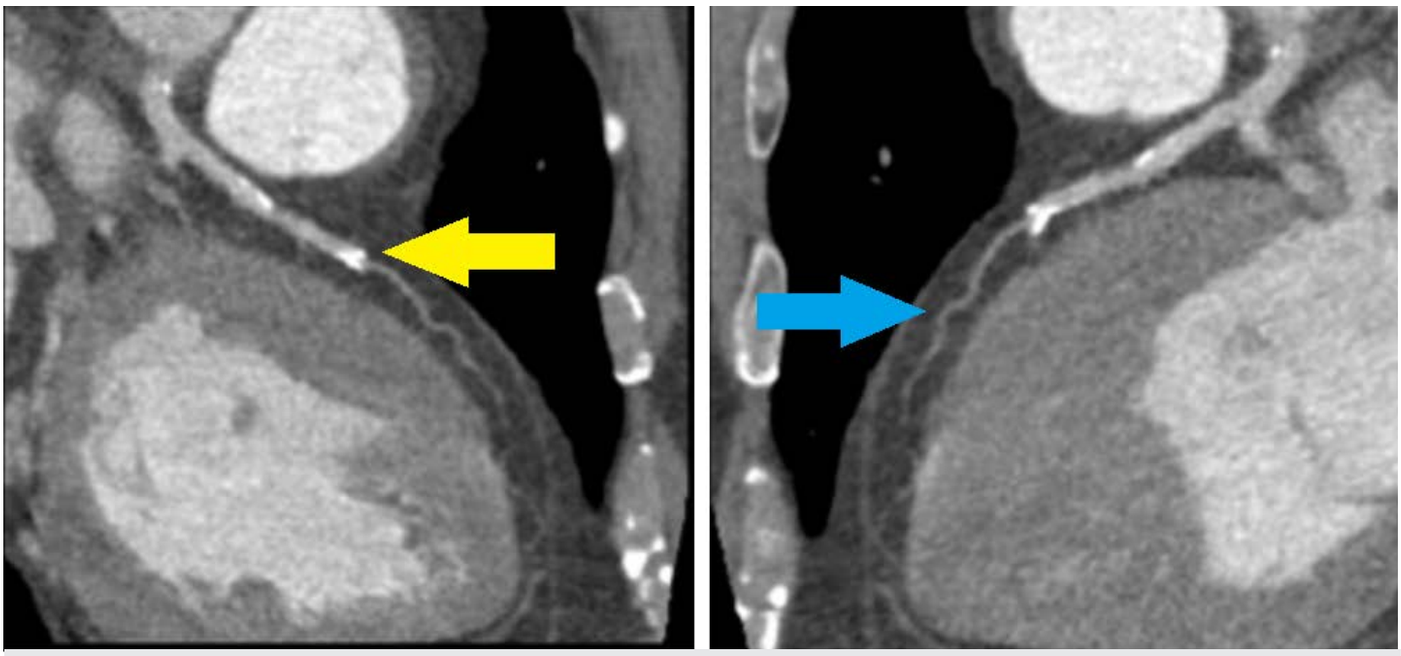

Figure 3.
Follow-up CTA of left anterior descending artery (LAD) shows a severe mid-LAD lesion with calcified plaque (yellow arrow) and small distal LAD (blue arrow).

using CTA as a starting point because it does not provide a functional assessment. Thus, it is essential to use stress tests in conjunction with CTA to provide the functional assessment of whether or not the lesions picked up by CTA merit treatment until CTA FFR (fractional flow reserve) becomes main stream for clinical use.

TREATING CAD IN WOMEN

For both men and women who have obstructive CAD, coronary artery bypass grafting (CABG) and coronary stenting are the most common methods of treatment. However, women with CAD often suffer more complications, such as higher risk of bleeding and higher rate of in-hospital mortality. Duvernoy's research indicates that these disparities are due to women's smaller average body mass and higher prevalence of renal insufficiency, which is more common in older women (who also tend to be the group most likely to present with CAD). "Once you correct for size—body surface area—and baseline renal insufficiency, you remove a lot of the gender gaps or disparities in treatment outcomes," she says.

Nonobstructive CAD poses a larger problem, both in terms of diagnosis and treatment. Perdoncin explains, "Nonobstructive CAD is a phenomenon that's more unique to women. We don't have as much information about how to treat that, and patients who present in that setting don't necessarily get the appropriate, evidence-based treatment."

The lack of widespread information on treating nonobstructive CAD is a source of frustration for some physicians. "It's harder to treat someone when you can't just put in a stent and fix it," says Duvernoy. "That's what's frustrating for providers who don't necessarily know what to do with women who present with chest pain but have clear coronary arteries. Physicians end up, in a figurative sense, throwing up their hands and saying, 'I don't know what to do, so I'm not really going to do anything.'"

That being said, nonobstructive CAD is treatable. Lifestyle modification (exercise, diet, weight loss) can be very helpful, and there are pharmacological therapies available to help relieve symptoms and improve vascular function.

Diagnosing and treating women presenting with chest pain can be challenging for even the most experienced clinician. It requires a little more sleuthing compared to treating symptomatic men, but the most important thing is not to give up and assume that nothing is wrong.

"It's a matter of reframing your mind to be aware that women can have these syndromes," says Duvernoy. "The diagnosis might be a little more difficult, but that doesn't mean you should discount what they're coming to you with."

Conflict of Interest Disclosure:
Laura Gerik is assistant managing editor and Ryan Chang is an intern at the *Methodist DeBakey Cardiovascular Journal*.

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