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Gender and Microvascular Angina

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Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in women, and is responsible for more deaths in women than in men [1]. Under-recognized gender differences in the presentation, diagnosis, management and pathophysiological mechanisms of cardiovascular disease often lead to missed diagnoses of this disease in women. Chest pain and other symptoms suggestive of myocardial ischemia in women represent an area of significant economic and health-related burden. Up to 50% of women compared to only 17% of men undergoing coronary angiography for the evaluation of ischemia are found to have normal or insignificant CAD [2]. In this era where identifying the “culprit” obstructive lesions in the epicardial coronary arteries defines the diagnosis of symptomatic coronary artery disease, women may be regarded as having “non-cardiac” pain. These same women often continue to have symptoms, resulting in increased morbidity and associated with increased mortality, both a heavy economic toll [3]. Contemporary work demonstrates that these women may have microvascular angina (MVA), a dysfunction in the coronary microcirculation, as a cause for chest pain and ischemia with nonobstructive coronary arteries. This review will relate the gender differences experienced by women with cardiac-related chest pain syndromes to female specific pathogenetic mechanisms in MVA.

Gender Differences

Chief Complaint: Chest Pain

Women present for evaluation of chest pain more often than men [2]. Chest pain in women is often described as “atypical” even in the setting of acute coronary syndromes (ACS). Whereas typical chest pain is characterized by retrosternal pain that is brought on by exertion and relieved by rest or nitroglycerin, atypical chest pain often represents discomfort in the arm, neck, jaw, or epigastrium with no relation to activity. This pain may last for hours, be reproducible on palpation, and differ in severity or quality to previous episodes of chest pain.

A subgroup analysis of the ACS registry at the University of Michigan showed diaphoresis was more common in men while nausea was more common in women in the setting of ACS. Women were also more frequently reported to have emesis and jaw, neck, and back pain [4]. Shortness of breath, paroxysmal nocturnal dyspnea, indigestion, loss of appetite, cough, dizziness, weakness, fatigue, and palpitations are noted to be more common in women as well [5, 6]. However, there have also been numerous other studies showing no gender differences [7–9]. Milner *et al.* [10] suggested that gender differences in symptoms may in part be attributed to women being better communicators and being more likely to verbalize symptoms that men consider trivial.

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In a large study of 20,881 patients admitted with ACS, 8.4% did not complain of chest pain at all. These patients were more likely to be female, older, or have comorbid conditions such as diabetes mellitus, hypertension, or congestive heart failure [11]. In a cumulative review of all studies from 1970–2005 reporting ACS symptom presentation, women were noted to have ACS without accompanying chest pain or discomfort more often than men [5]. This could lead to a delay in diagnosis and treatment. However, the importance of female gender in predicting MI without chest pain disappeared after multivariate analysis in another study [12].

The clinical importance of symptom presentation taken alone, or lack thereof, is illustrated by angiographic data from WISE [2] in which less than half of the women who reported typical angina had angiographic CAD. In another study by Sullivan *et al.* [13], virtually 100% of men with the complaint of chest pain referred for angiography were found to have significant CAD as compared to only 59% of women. This suggests chest pain or discomfort is a less specific, and possibly less sensitive, marker for ischemic heart disease in women compared to men. As such, it is a difficult challenge to make the diagnosis of ACS by symptomatology alone. The lack of firm consistent data only allows physicians and healthcare workers to take into account the totality of symptoms and how it plays into an overall “bigger picture.” Simply recognizing that gender and atypical presentations certainly play a role in ACS seems to be the bottom-line.

Diagnosis: Nonobstructive CAD in an Obstructive CAD World

Current diagnostic tools to evaluate CAD are based on the concept that cardiac ischemia is caused by “significant” obstructions in the major coronary arteries (>50% stenosis by angiography). However, of the 450,000 women undergoing cardiac catheterization each year, up to 50% are found to have non-obstructive lesions [1]. Thus, gender-specific issues arise with each diagnostic modality in the assessment of chest pain and CAD.

The ECG treadmill test, one of the most widely utilized CAD risk stratification tool, has lower sensitivity and specificity in women (60–70%) when compared to men (~80%) [14–17]. This may in part be due to the lower pretest probability for CAD in women. However, other reasons include conditions more frequently found in the female population such as cardiac syndrome X, mitral valve prolapse, and coronary vasospasm. Digoxin-like effect of endogenous estrogen, which naturally fluctuates during the menstrual cycle, can also influence ECG findings. Observations that women are more often unable to achieve maximal levels of exercise and that they demonstrate lower QRS voltages detracts from the diagnostic accuracy as well. However, the ECG treadmill test should not be discounted entirely as some findings on ECG are highly predictive of CAD in women. Holubkov *et al.* [18] found that inferior Q waves and symmetrical T-wave inversions were independent and highly specific indicators of CAD in a group of 585 women complaining of chest pain with no prior history of CAD. Evidence of ventricular repolarization, most notably wide QRS/T angle and prolonged QT, were significant predictors of future cardiac events and mortality in 38,000 postmenopausal women from WHI [19]. Widened QRS and QTrr interval and a more depressed ST-segment in precordial lead V5 are also known predictors in women with suspected myocardial ischemia [20]. Other information obtained from an exercise treadmill test, such as exercise duration, exercise capacity, and METs, can also be used for prognostication. Achieving less than 5 METs poses increased risk for cardiac events [21].

Women with insufficient exercise capacity are usually referred for pharmacologic stress imaging to detect perfusion or wall-motion abnormalities. These tests have higher diagnostic accuracy compared to electrocardiography. The average sensitivity and specificity for stress SPECT is 81% and 66%, respectively. Results are similar for stress echocardiography with a sensitivity of 84% and a slightly higher specificity of 76% [22]. Despite the unique

limitations posed by women, such as breast tissue artifact and smaller left ventricular size, both imaging modalities prove to be equally accurate in diagnosing and risk stratifying women as compared to men [23–26].

In cardiac syndrome X (CSX), more commonly seen in female patients, noninvasive stress testing may be of lesser utility. Wall motion abnormalities have not been demonstrated in patients with chest pain and normal coronary arteries [27, 28]. Dobutamine stress echocardiography is often normal, specifically, in women with single-vessel disease or those with evidence of microvascular or endothelial dysfunction [29]. This brings up an interesting point: either ischemia does not play a role in CSX or current methods lack the ability to detect small perfusion abnormalities or ischemia in subendocardial and subepicardial myocardium. Cardiac MRI, with its superior assessment of anatomy, soft tissue, blood flow, and left ventricular function, has been utilized to demonstrate subendocardial ischemia in women with angina and nonobstructive CAD [30]. Phosphorous-31 NMR spectroscopy can detect metabolic evidence of ischemia by quantifying the ratio of high-energy phosphates. A reduced ratio of phosphocreatinine and ATP, which points to a shift toward anaerobic metabolism, was observed during mild handgrip exercise in 20% of women with chest pain and normal coronary arteries [31]. This finding had prognostic significance in a subsequent study where patients with no CAD and abnormal MR spectroscopy had similar cardiovascular event rates when compared to those with CAD [32].

Management: Do Physicians Exhibit Gender Bias?

After we employ our clinical acumen to triage patients down the correct path of diagnostic assessment, how much do our own biases affect management? The data in this area is conflicting with some studies demonstrating a true gender bias with regard to the diagnostic, therapeutic, and preventative measures offered to female patients, while others do not [33–35]. For the most part, recommendations to prevent CVD in women do not differ from men. That being said, women are less likely prescribed aspirin, beta-blockers, and lipid lowering therapy as secondary preventive measures [36–40]. It has been reported that women are treated less aggressively and referred for cardiac catheterization less frequently. During the evaluation of angina to acute MI, women were more likely to be discharged from the emergency department [41] and less likely to receive heparin, ACE inhibitors, aspirin and glycoprotein IIb/IIIa inhibitors [42, 43] as well as invasive procedures [40, 43–46].

Lack of awareness among women and physicians alike may play a role in the gender disparities. Only 55% of women surveyed in 2006 indicated heart disease as the leading killer of women. In contrast, 63.1% of women identified heart disease as the leading cause of death in men. Women are also unaware of healthy levels of risk factors and tend to underestimate their personal risk for CVD. Awareness of risk correlates to preventive action taken by the patient to lower risk. Interestingly, 38% of women cite lack of physician-initiated discussions as their reason for not speaking to their doctors about their CVD risk [47]. In fact, physicians perceive women to be at lower risk for CVD despite similar calculated risk as men [48]. Less than 20% of physicians know that more women than men die of CVD. In addition to lack of awareness, physician age, subspecialty, years in practice, clinical inertia, and external barriers have been cited as reasons for lack of adherence to guidelines [49, 50].

Prognosis

Does the summation of gender disparities at each step in the care of women presenting with chest pain result in worse outcomes for women? Cardiovascular deaths in women outnumber men by 50,000 [1]. Some studies have shown that less aggressive treatment and revascularization rates in women result in increased reinfarction and mortality [40, 51].

After adjustment, other studies show similar outcomes between men and women, despite women having less extensive coronary disease, better left ventricular function, and no prior MI [52, 53]. On the other hand, women are older with a greater number of comorbidities such as diabetes mellitus, hypertension, and congestive heart failure [41, 43, 52]. This may certainly contribute to the observed higher mortality, but other pathophysiologic mechanisms may be at work, especially when considering that prognosis is equally poor between those with and without obstructive CAD. Within 5 years of a first MI, women have higher rates of recurrent MI, fatal CHD, stroke, heart failure, and sudden death compared to men [1]. Persistent chest pain and nonobstructive CAD in women, previously thought to be a low-risk subgroup, similarly portends poor prognosis with a 3-fold increase in 5-year annualized cardiovascular event rate compared to asymptomatic women [54]. The gender disparities are apparent, yet the underlying mechanisms have not been fully elucidated. The interplay of vascular health, abnormal nociception, and hormonal imbalances may pose a unique milieu for the development of CVD in women.

MVA: A New Paradigm

Cardiac syndrome X gained widespread recognition around 1973 as chest pain with evidence of myocardial ischemia in the absence of obstructive coronary artery disease [56]. A subset of these patients who go on to have abnormal coronary reactivity testing are thought to have “MVA” to describe myocardial ischemia in the presence of coronary vascular dysfunction. The fact that more women than men are diagnosed with CSX, suggests a gender-specific pathophysiology. The fact that those women are more commonly menopausal, implicates estrogen deficiency as an underlying mechanism. Though the exact pathogenesis eludes us, abnormal nociception, endothelial dysfunction, and inflammation are all probable contributors to the pathogenesis of MVA. However, estrogen, with its effects on vascular health, allows us to consider gender as an important risk factor in the development of microvascular dysfunction. MVA represents an emerging concept in cardiovascular health for women.

Abnormal Nociception

Myocardial ischemia is questioned as an underlying cause for chest pain in MVA. Not all patients demonstrate evidence of myocardial ischemia on stress testing [27, 57, 58]. Whether that is a function of the insensitivity of current diagnostic modalities, as previously mentioned, or evidence of alternate pathophysiologic mechanisms is a valid concern. However, several studies suggest mechanisms for chest pain are rooted in altered pain perception and processing at the level of both the peripheral and central nervous systems.

Patients with chest pain and normal coronary arteries demonstrate increased pain sensitivity to a number of stimuli. Intracardiac catheter manipulation [59, 60], infusion of vasoactive [57, 61] and non-vasoactive substances [59, 60], and atrial and ventricular pacing [60] can reproduce chest pain symptoms in these patients suggesting multiple mechanisms at work. Mechanical distortion of cardiac mechanoreceptors may explain the response to physical stimuli such as intracardiac catheter manipulation [62]. Sensitivity of cardiac chemoreceptors to adenosine, dipyridamole, epinephrine, normal saline, and contrast medium may be involved. Lagerqvist *et al.* [63] demonstrated patients with anginal pain and normal coronary arteries have lower threshold for adenosine-induced chest pain when compared to patients with CAD and normal controls.

In addition to abnormalities found at the somatic level, imbalances within the autonomic nervous system contribute to increased pain sensitivity. Dysfunction in cardiac adrenergic nerve fibers is found in 75% of CSX patients [64]. At the same time, two thirds of CSX patients have impaired parasympathetic tone [65]. The resulting imbalance increases

microvascular tone and sensitivity to vasoconstrictor stimuli. Whether this perpetuates the existing microvascular dysfunction or is a result of it is not quite clear. It is quite possible that these alterations in afferent and efferent nerve fiber functioning can explain not only increased pain sensitivity, but also endothelial dysfunction.

Rosen *et al.* [66] hypothesized that the handling of afferent nerve signals by an altered central processing system in CSX could explain differences in pain perception outside of myocardial ischemia. CSX patients, while demonstrating chest pain in the absence of myocardial ischemia as assessed by dobutamine stress echocardiography, had greater cortical activation when compared to normal controls. Thus the thalamus, acting as a gate to afferent signals fired as a result of myocardial stretch during increased cardiac work, is fundamentally altered in CSX patients. Valeriani *et al.* [67] demonstrated CSX patients maintained the amplitude of the N2/LEP component through repeated sequences of painful stimuli, reflecting inadequate habituation of cortical pain processing. This may support the prolonged angina and persistence even after cessation of exertional activities experienced by CSX patients.

Endothelial Dysfunction

The endothelium maintains vascular homeostasis through control and release of various vasoactive substances in reaction to hemodynamic change, in addition to its other roles in platelet aggregation, thrombosis, and regulation of vascular permeability. The imbalance of vasodilatory and vasoconstricting forces and the consequential induction of inflammatory and proliferative changes in the vasculature comprises the core pathogenesis in endothelial dysfunction. Such pathology in the coronary microvasculature is a proposed mechanism for MVA, chest pain in the absence of obstructive CAD.

Vasodilatory forces are largely determined by EDRF-nitric oxide system. Numerous stimuli are known to act on this system to cause vasodilation. Acetylcholine causes vasodilation via muscarinic receptors that stimulate synthesis and release of the endothelium-derived relaxing factor, nitric oxide (NO), from an intact endothelium. At higher doses it causes vasoconstriction by direct action on smooth muscle cells. In the presence of endothelial dysfunction, the low doses of acetylcholine that cause vasodilation can equally produce vasoconstriction. In CSX, intracoronary infusion of acetylcholine, and not papaverine or nitrate, leads to lower increases in coronary blood flow when compared to controls, suggesting blunted endothelium-dependent microvasculature dilation and enhanced microvascular constriction [68–70]. This imbalance is likely further enhanced by the basal decrease in NO levels [71] and elevated levels of endothelin (ET), a potent vasoconstrictor with several isoforms [72]. Endothelin-1 (ET-1) is the predominant isoform produced by the vascular endothelium. Acute intravenous infusion of L-arginine, a precursor of NO, decreases this isoform and enhances nitrate (NOx) release [73]. Vascular homeostasis is not only influenced by the net effect of known vasoactive substances, but by gender as well. Cox *et al.* [74] showed that elevated ET activity and female gender were both independently associated with a reduction in coronary vascular resistance. This would predict that women with high ET levels have the smallest percent change in CVR. In contrast, when ET levels were assessed using more sensitive immunoassays, there were no baseline difference in ET-1 levels in CSX and controls. CSX patients did however exhibit greater levels of ET-1 release in response to glucose loading suggesting that stressful stimuli triggers an enhanced vasoconstrictor response [75].

The disrupted homeostasis of the coronary microvasculature promotes a proinflammatory milieu that further contributes to endothelial dysfunction found in MVA. Thus, pro-inflammatory cytokines, cell adhesion molecules, and growth factors are active to a greater extent under a dysregulated endothelium. C-reactive protein (CRP), intercellular cell

adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), are found at higher levels in CSX [76, 77]. Consistent with that finding, Li *et al.* [78] reported elevated levels of, not only the systemic inflammatory marker CRP, but interleukin-6 (IL-6) as well as two systemic inflammatory cell indexes, white blood cells and monocytes in female patients with CSX. Elevated CRP levels may blunt the systemic endothelial vasodilator response [79] and attenuate endothelial-dependent NO production [80]. This translates to clinically relevant findings. Cosin-Sales *et al.* [81] correlated higher CRP levels to more frequent and prolonged chest pain episodes, positive exercise stress tests, and ischemic episodes during 24-hour Holter monitoring. Endothelial-dependent increases in coronary blood flow induced by acetylcholine were reduced in patients with higher CRP levels. However, the association of high CRP levels and microvascular dysfunction, as defined by coronary flow reserve < 2.5, has only been shown in patients with CAD [82, 83]. Despite this, it is still likely that inflammation has some role in promoting or even causing endothelial dysfunction.

Estrogen Deficiency

Estrogen, with its effects beyond female sexual development and reproduction, links the pathogenesis of MVA to the female gender. Women are suspected to develop CVD later in life when compared to men due to the protective effects of estrogen on the cardiovascular system. Estrogen has a positive effect on lipid profiles by stimulating production of HDL cholesterol and reverse cholesterol transport [84], which results in decreased LDL cholesterol, and increased HDL cholesterol and triglycerides [85]. Estrogen deficiency is associated with decrease in insulin sensitivity and increase in insulin resistance [86]. Menopause is associated with abnormal endothelial function of the coronary microvessels. Whether the estrogen deficiency causes the endothelial dysfunction in MVA or simply represents a concomitant stressor to the pre-existing endothelial dysfunction is unclear. Estrogen exhibits a vasodilatory effect on vascular tone by facilitating smooth muscle relaxation. Roque *et al.* [87] demonstrated the beneficial effects of estrogen in postmenopausal women with CSX. In 15 postmenopausal women with angina and normal coronary arteries, 14 women experienced vasoconstriction in reaction to acetylcholine. Twenty-four hours after placement of transdermal estradiol, when premenopausal estradiol levels were achieved, repeat coronary reactivity testing demonstrated vasodilation with acetylcholine infusion in 12 women, and modest decrease in vasoconstriction in 2 women. This enhancement of endothelial function may be due to increased release or production of relaxing factors from the endothelium. It has been hypothesized that estrogen may provide an antioxidant effect, reducing reactive oxygen species like superoxide anion, which would otherwise be free to scavenge NO [88]. The increased vasodilatory reserve can translate to an anti-ischemic effect. Transdermal 17 β -estradiol decreases frequency of chest pain episodes [89] and decreases exercise-induced angina and ST-segment depression [90] in postmenopausal women with CSX. Estrogen's beneficial effects seem to be gender-dependent, as men do not experience the same improvements in endothelial function and coronary blood flow [91].

Estrogen may also play a role in abnormal nociception described in MVA. Women are noted to be more sensitive to pain stimuli, which can correlate to variations with the menstrual cycle. Diffuse noxious inhibitory control, an endogenous pain control mechanism that inhibits nociceptive activity, varies throughout the menstrual cycle with the lowest activity during menstrual and luteal phases. The attenuated DNIC did not correlate strongly to levels of estrogen or progesterone, but it suggests sex hormones in general may modulate pain in women [92]. Other studies evaluating pain thresholds and hormonal fluctuations during the menstrual cycle have yielded inconsistent results [93, 94]. This can be attributed to different

pain stimuli applied, whether temperature, pressure, electrical, ischemic, and the methods by which menstrual cycle were measured.

The gender differences in chest pain perception may be attributed to baseline differences in the endogenous opioid receptor system and additional effects from the absence of estrogen.

-endorphin, which acts on μ -opioid receptors, induces analgesia with adenosine-provoked chest pain in male but not female subjects [95]. This may suggest baseline differences in endogenous analgesia. In the rodent model, female rats exhibit less vigorous endogenous opioid-mediated analgesia than males. The disparity appears to be exacerbated by ovariectomy. Similarly, during a low estradiol and progesterone state mimicked during the follicular phase of menses, women demonstrated reduced activation of the μ -opioid system. This resulted in reduction in endorphin release and more intense pain reported by female subjects [96]. A high estradiol state in women resulted in greater activity of μ -opioid receptor mediated neurotransmission when directly compared to a low estradiol state [97]. Therefore, a deficiency of estrogen may result in decreased endogenous analgesia. As suggested by Rosano *et al.* [89], estrogen may also have a direct anti-anginal effect through attenuation of the algogenic effects of adenosine to induce ischemic-like chest pain.

Treatments

Anti-anginal Therapy

Current treatments for MVA focus on symptomatic management of chest pain and improvement of underlying endothelial dysfunction. Traditional anti-anginal therapy including nitrates, beta-blockers, and calcium channel blockers are the mainstay of therapy targeting ischemia in the coronary microvasculature. Nitrates seem to be less effective in chest pain with normal coronary arteries, with observational studies showing chest pain relief in only 42% of patients [58]. Despite this, nitrates have been shown to improve time to angina and peak ST-segment depression in CSX [98]. Large randomized control trials need to be performed to clarify the utility of nitrates in the short and long-term treatment of chest pain with normal coronary arteries. In the meantime, nitrates are still widely used. Beta-blockers are considered first-line therapy in CSX. Their ability to decrease myocardial demand and adrenergic tone leads to decrease in anginal symptoms and ischemic ECG changes [99]. Nebivolol, a highly selective β_1 -antagonist, also exerts beneficial effects, but by a different mechanism which targets the underlying endothelial dysfunction. It has been shown to increase NOx (nitrite + nitrate) and superoxide dismutase levels while lowering myeloperoxidase and malondialdehyde levels [100]. The net effect is decreased oxidative stress and improved endothelial function. Calcium channel blockers have variable symptomatic relief and improvement in ischemia. Nifedipine reduces angina, improves exercise tolerance, and decreases ST-segment depression [101, 102]. Contrastingly, verapamil did not demonstrate the same beneficial effects when directly compared to propranolol [103].

Antioxidant & Anti-inflammatory Therapies

Newer treatments including ACE inhibitors, statins, and biguanides reduce oxidative stress on microvasculature to improve endothelial function and increase coronary blood flow. Long-term ACE inhibitor therapy shows similar improvements on exercise duration and exercise-induced myocardial ischemia as anti-anginal therapies. The mechanism has been linked to improved endothelial function by increased NO bioavailability. Enalapril reduced ADMA, a NO synthase inhibitor, and increased NOx and L-arginine/ADMA ratio. In these patients with CSX, coronary flow reserve increased indicating improvement in coronary microvascular function [104]. ACE-I in combination with statins also improves endothelial-dependent coronary flow reserve and reduces oxidative stress. Flow mediated dilation of the

brachial artery increased while levels of an anti-oxidant enzyme, superoxide dismutase (SOD), were lower after treatment suggesting ACE-I plus statin therapy decreased the oxidative stress on the microvasculature [105]. Decreased insulin resistance, as with metformin therapy, has been shown to improve endothelial-dependent vascular function in nondiabetic women with CSX [106].

Treatment of Abnormal Nociception

In patients with abnormal nociception, imipramine and neurostimulation may prove beneficial. Cox et al [107] showed women with chest pain and normal coronary angiograms who were refractory to standard anti-anginal therapies had reduced chest pain episodes. This is consistent with the use of tricyclic antidepressants in other pain syndromes such as diabetic neuropathy and migraine headache. The inhibition of norepinephrine re-uptake by pain-modulating neurons may lead to visceral analgesia. Spinal cord stimulation has also been used as a treatment for persistent chest pain by modulation of pain transmission. SCS improves otherwise refractory angina and ST-segment depression induced by DST and recorded by 24 hour Holter monitor in CSX [108]. SCS may work by modulation of pain processing at the level of the inhibitory neurons in the posterior horns of the spinal cord and more centrally as previously described. SCS may also have an anti-ischemic effect, improving cardiac efferent nerve fiber functioning.

Hormone Replacement Therapy

Despite the improvements in endothelial function with estrogen in postmenopausal women, hormone replacement therapy (HRT) is not a standard therapy for MVA. Because of recent evidence demonstrating the negative effects in women, such as increased risk for coronary events, stroke, and venous thromboembolism, HRT is not recommended for primary or secondary prevention of CVD. Data regarding the use of HRT in CSX has not been confirmed in any large trials.

Conclusions

It is apparent that there are important gender differences in the presentation, diagnosis, prognosis and treatment of chest pain. Current approaches stratify chest pain according to cardiac or non-cardiac by diagnostic tools and treatment is employed targeting the underlying etiologies. Due to gender difference, each step can have shortcomings, which, to the detriment of women, could lead to misdiagnosis or mismanagement. While some data suggest that women may simply exhibit inherent differences in how they report or cope with chest pain, additional data indicate that disparities are rooted in under-recognized gender-specific pathophysiologies. MVA appears to represent one such pathophysiologic mechanism. When framed in the context that coronary obstructions constitute significant CAD, non-obstructive chest pain in many women may be inappropriately triaged. Acknowledging an association between gender and an underlying cardiac etiology for chest pain may result in improved morbidity and mortality for women. Further research needs to be conducted in the specific areas of microvascular coronary disease, the etiologies, diagnosis, and management.

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Figure 1.

From the National Institutes of Health-National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation (WISE) study, persistent chest pain predicted CV events in women without obstructive CAD. Reprinted from Johnson *et al.* [55]