Chapter 3
Gender Differences in Clinical Manifestation and Pathophysiology of Ischemic Heart Disease- A Gender Paradox

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Introduction

This chapter will cover the basic pathophysiology and symptom presentation of ischemic heart disease and will highlight the differences in heart disease between men and women. Heart disease affects millions of Americans and is the leading cause of death for both men and women in America [1]. Numerous risk factors for developing heart disease and the mechanisms by which a normal heart becomes a diseased heart have been previously identified. Coronary atherosclerosis leading to obstruction of the epicardial coronary arteries has been identified as the leading cause of heart disease. With this paradigm of coronary artery disease (CAD) in mind, clinicians typically evaluate and treat patients with angina with medications or interventions aimed at preventing or correcting obstructive CAD.

More recently, there have been observed differences in the incidence, prevalence, and burden of heart disease between men and women. This includes three striking observations: women have a higher prevalence of angina, a lower burden of obstructive CAD on angiography despite as many, if not more, traditional risk factors, and a worse prognosis for heart disease compared to men. All three of these observations are in the setting of a lower prevalence of obstructive CAD compared to men [2, 3]. Together, these observations have been termed the "gender paradox," which cannot be explained solely with the pathophysiology of obstructive CAD. This gender paradox has led to the postulate that ischemic heart disease is different in women and in men in its pathogenesis, symptoms and prognosis. To further the understanding of heart disease in women, the National Heart, Lung, and Blood Institute (NHLBI) created an initiative which resulted in the Women's Ischemic

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Symptom Evaluation (WISE) study [4, 5]. The NHLBI-WISE is a prospective cohort study designed to study gender differences in ischemic heart disease. It recruited women that were referred for diagnostic angiography for symptoms of ischemic heart disease. A total of 936 women were recruited and then followed over time. Numerous studies and sub-studies have been analyzed on data collected from this cohort, which has contributed vastly to our understanding of differences in ischemic heart disease between men and women.

In looking at the numbers of patients presenting to medical care with angina, a certain percentage will not have clinically significant obstruction of the coronary arteries. When comparing the sexes, women presenting with stable angina symptoms have been reported to have a significantly lower incidence of obstructive CAD than men (48 % vs. 67 %) with an impressive odds ratio of 0.37 for women compared to men [6, 7]. Evaluation of women with angina but without obstructive CAD on coronary angiography with phosphorus-31 nuclear magnetic resonance spectroscopy, a non-invasive imaging technique that measures aerobic and anaerobic metabolites to tell if a tissue is ischemic, interestingly revealed that 20 % will still have evidence of myocardial ischemia, suggesting microvascular disease involvement [8]. Clinically, this subset of women has worse cardiovascular outcomes compared to women without evidence of ischemia [3]. Consequently, the nomenclature of Ischemic Heart Disease (IHD) has been suggested as a better term than CAD in order to encompass these patients with poor outcomes from heart disease who do not exhibit obstructive CAD [8, 9].

A further concern with gender differences and heart disease is the difference in perception and reporting of myocardial ischemia. “Typical Angina” has been classified as symptoms of pain in the chest that are aggravated by exertion and relieved by rest or nitroglycerine. Chest pain that does not follow this pattern is termed either atypical angina or non-cardiac chest pain. Unfortunately, women have long been underrepresented in studies of heart disease. Studies of women with proven heart disease have revealed that women frequently describe their angina pain in ways that do not fall under the classification of “typical angina” [10].

Gender Differences in Clinical Manifestation of IHD

The presentation of IHD in women is frequently more complex and multifactorial than that in men. Due to the difference in presentation of ischemic heart disease in women, the diagnosis and treatment of ACS in women in the pre-hospital setting as well as emergency department may be sub-optimal, resulting in missed diagnoses, delays in treatments, and excess mortality [11, 12]. The following section will review typical angina and atypical angina and will then highlight some of the differences between symptoms typically reported by men and women.

Typical Angina Symptoms

Obtaining a clinical history has long been the most valuable tool in the clinician’s diagnostic arsenal. Unfortunately, symptoms of cardiac ischemia vary between

patients which can make clinical diagnosis challenging. In order to have a common language for evaluating patients, the terms typical angina, atypical angina, and non-anginal chest pain have been standardized in the literature [13]. Three clinical questions help to classify a patient's symptoms of chest discomfort: Is the discomfort sub-sternal? Is it precipitated by exertion? And, is there prompt relief with rest or nitroglycerine? If the patient's symptoms affirmatively follow all three of these clinical features, the symptoms are classified as "typical angina." Having two of the features classifies symptoms as "atypical angina," and having only one or none of the features classifies symptoms as "non-anginal." This system has been applied to a group of patients that underwent cardiac catheterization to determine how the symptoms correlated with presence or absence of obstructive CAD. The resulting data helped clinicians to assign a pre-test probability for obstructive CAD to patients based on age, sex, and classification of angina. Women were found to have a lower incidence of CAD compared to men of similar age and with similar angina classification with the notable exception of post-menopausal aged women with typical angina. While this classification of angina has proven to be hugely useful in the study, diagnosis and treatment of coronary disease, two limitations should be kept in mind when evaluating the history provided by women. The first is that it applies only to obstructive CAD that can be seen on angiography and was not developed to assess for microvascular disease. The second is that it places large emphasis on the symptom of chest pain. Other studies looking at prediction models for the prevalence of obstructive CAD in women based on symptom classification, age, and gender have found that women have significantly less obstructive CAD than would be predicted [14, 15].

Figure 3.1 reproduces the Diamond probability of coronary artery disease compared with actual observed coronary disease prevalence in symptomatic women from the National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation (WISE) [14].

Symptoms Reported by Women

While both men and women will frequently report symptoms such as chest pain or pressure, symptoms reported by women also frequently fall into the classification of atypical angina or non-angina pain rather than typical angina. This can make it challenging for clinicians to accurately estimate their pretest probability of heart disease. It is important to have an appreciation for the variation in angina symptoms between men and women. Women are more likely to have angina at rest, during sleep, or with emotional or mental stress. They are also more likely to have symptoms such as neck and shoulder pain, nausea, vomiting, fatigue or dyspnea during an acute myocardial infarction [16].

Research on gender differences in symptoms has highlighted distinct differences in disease presentation. An observational study [17] of over one million patients with myocardial infarction demonstrated that while 70 % of men complained of chest pain, only 58 % of women complained of chest pain. Interestingly, this difference was most pronounced in younger women, and was not statistically significant in older women. While chest pain is certainly present in the majority of women with

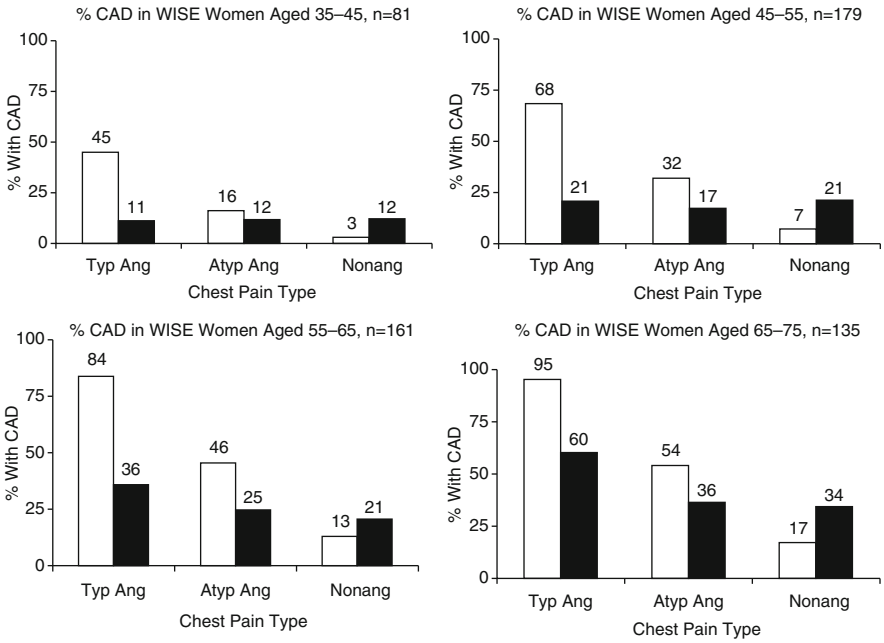

Fig. 3.1 From the National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation (WISE), the Diamond probability of coronary artery disease (*open bars*) compared with actual observed coronary disease prevalence in symptomatic women (*solid bars*). *Atyp Ang* atypical angina, *Nonang* non-angina, *Typ Ang* typical angina (Reprinted from "Shaw et al. [14] with permission from Elsevier)

acute myocardial infarction, one study [18] demonstrated high rates of other symptoms including shortness of breath (58 %), weakness (55 %), and fatigue (43 %). Non-chest pain symptoms during the prodromal time leading up to a myocardial infarction were also frequently experienced. Notably, unusual fatigue (70 %), sleep disturbance (48 %), and shortness of breath (42 %) were more prevalent than chest discomfort (30 %). While actual symptom rates vary throughout the literature, the variety of non-chest pain symptoms in women remains impressive. A list of many of these common "atypical symptoms" is included in the Table 3.1 [10, 18–20].

Awareness of the variety and frequency of symptoms other than chest pain is important for patients so that they might seek medical attention in a timely manner. Early recognition and treatment of an acute coronary syndrome can clearly improve outcomes, but disturbingly a recent review of emergency medical services found that only 23 % of patients call 9-1-1 when experiencing an acute coronary syndrome [21]. It is also important for clinicians to recognize symptoms so that they can appropriately diagnose and treat women presenting with cardiac ischemia. While a history of typical angina symptoms is frequently associated with obstructive CAD in both men and women, a history of atypical angina in a woman with the aforementioned symptoms should also warrant careful consideration by the clinician. Even in the absence of obstructive CAD, advances in diagnostic technology are increasingly

Table 3.1 Variety of symptoms reported by women during ACS

Chest pain
Neck/jaw/tooth pain
Arm/shoulder/back pain
Cold sweat
Hot/flushed
Fatigue
Weakness
Cough
Heart racing/palpitations
Shortness of breath
Loss of appetite
Indigestion/nausea/vomiting
Arm numbness or burning
Dizziness/lightheadedness
Vision change
Headache

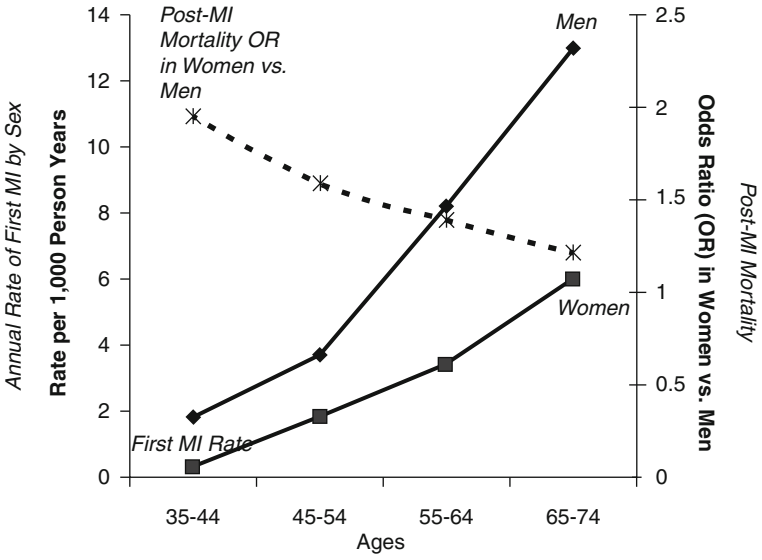

Fig. 3.2 Disparity between the lower incidence of myocardial infarction and worse outcomes in women compared to men (Reprinted from Merz. et al. [22] with permission from Elsevier)

identifying evidence of cardiac ischemia in symptomatic patients. This recognition of a pathophysiology for cardiac ischemia other than obstructive CAD could help to bridge the gap between lower rates of obstructive CAD in women with their high rate of poor cardiovascular outcomes. It is still unclear whether differences in the rates of underlying cardiac pathophysiology can help to explain some of the differences in symptoms experienced between the sexes.

Figure 3.2 reproduces the disparity between the lower incidence of myocardial infarction and worse outcomes in women compared to men [22].

Pathophysiology of Ischemic Heart Disease

As mentioned in the introduction, there is a gender paradox in that women appear to have less obstructive CAD and yet worse cardiovascular outcomes compared to men. In order to solve this gender paradox, multiple pathologies in addition to obstructive coronary disease have been suggested as contributing to IHD. These include obstructive CAD, plaque morphology, microvascular dysfunction, endothelial dysfunction, inflammatory conditions, and hormonal influence as displayed in Fig. 3.3.

Obstructive Coronary Artery Disease

The heart is a muscular organ that receives its blood supply from the coronary arteries originating at the aorta. These coronaries run along the epicardium before feeding deep into the myocardium. The majority of coronary artery disease in both men and women arises from obstructive disease of the epicardial portion of these coronary arteries. Without adequate blood flow from the coronary arteries, myocardial tissue becomes ischemic and loses its ability to efficiently contract and conduct electrical signals. These vital epicardial arteries branch out from the aorta in similar patterns in both men and women, but women commonly have smaller coronary artery diameter and less collateral arteries branching off of the major epicardial coronary arteries than do men [23]. Obstruction of the coronary arteries is most attributable to the chronic accumulation of lipids in arterial walls by the process of atherosclerosis. Obstructive atherosclerosis is more commonly seen in men than

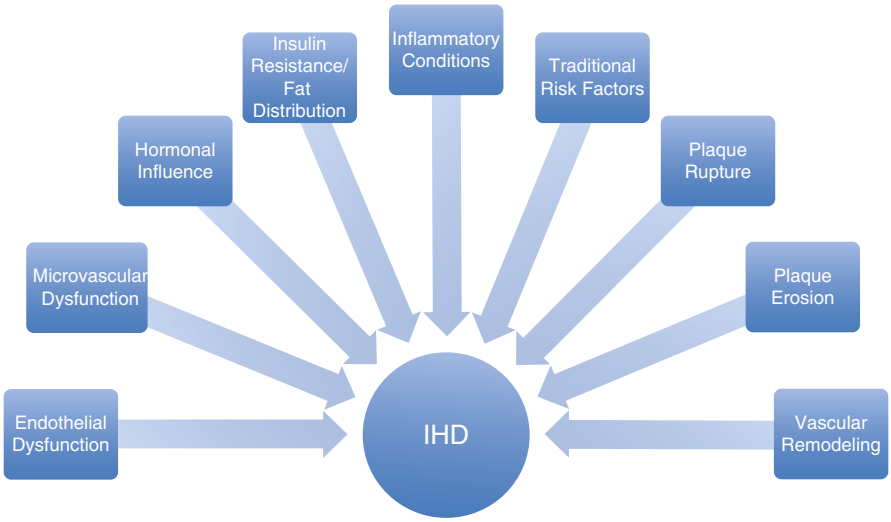

Fig. 3.3 Multiple factors contributing to Ischemic Heart Disease (IHD) in women

premenopausal women, but post menopausal women develop obstructive atherosclerosis at rates similar to those seen in men [24]. Major risk factors for the development of atherosclerosis include hyperlipidemia, hypertension, tobacco abuse, and diabetes mellitus. On a cellular level, in atherosclerosis, LDL deposited in the vessel walls triggers endothelial cells to signal monocytes. These monocytes differentiate into macrophages, which cross the endothelial wall and phagocytize the LDL particles. They then become lipid-laden foam cells that trigger smooth muscle cells to accumulate and develop a surrounding fibrous cap. With degradation caused by inflammatory cells, the fibrous cap can rupture, which uncovers the thrombogenic lipid core. This triggers thrombus generation, which can cause obstruction of blood flow through the artery and myocardial ischemia. Acute plaque rupture as well as plaque erosion and chronic narrowing from atherosclerosis can be seen on coronary angiography by injecting contrast dye and visualizing disruption in flow through the epicardial coronary arteries [25–28].

Plaque Erosion vs Plaque Rupture

Autopsies performed on women who died from sudden cardiac death reveal gender differences in plaque morphology. Lipid laden plaques with a necrotic core are more prevalent in men and, as discussed above, will typically rupture leading to sudden exposure of inflammatory cytokines and thrombus formation at the site of the plaque. Conversely, young women in particular have higher rates of plaques composed of smooth muscle and proteoglycan-rich matrix without a necrotic lipid laden core. In contrast to plaque rupture, these plaques without a necrotic core exhibit superficial erosion leading to thrombus formation. With plaque erosion, the core of the plaque remains intact and thrombi form after coming in contact with smooth muscle. Autopsies reveal thrombi at the site of plaque erosion as well as distal embolization of thrombi formed from plaque erosion [5, 29–32]. Importantly, these gender differences in plaque morphology tend to be most pronounced in younger pre-menopausal women whereas post-menopausal women generally have fewer differences in plaque morphology and incidence of obstructive CAD.

Remodeling

In response to atherosclerosis, coronary arteries undergo remodeling to preserve adequate blood flow. When plaques involve less than 40 % of the luminal area, “positive” or “outward” remodeling can lead to enlargement of the artery which preserves the intraluminal cross sectional area and blood flow [33]. Conversely, with “negative” or “inward” remodeling, the cross sectional area of the vessel is reduced and flow limitation is seen on coronary angiography. Whether a specific vessel will exhibit positive or negative remodeling continues to be an area of research, but some factors such as increased proteases from inflammatory cells seem to correlate with more positive remodeling [31]. Authors have suggested

increased amounts of positive remodeling in women compared to negative remodeling in men as a way to reconcile the more diffuse atherosclerosis, increased endothelial dysfunction, and increased microvascular dysfunction seen in women with the decreased amount of luminal obstruction observed on coronary angiography compared to men [14, 29, 31, 34].

Microvascular Angina

In contrast to angina secondary to obstruction of the large epicardial coronary arteries, microvascular angina (previously referred to as cardiac syndrome X) is a term used to describe angina symptoms from ischemia originating in intramyocardial microvascular arteries. As mentioned in the introduction of this chapter, women with chest pain presenting for angiography more frequently lack obstructive coronary artery disease than men presenting for angiography [6–8], suggesting that there is a pathology other than obstructive coronary disease responsible for their symptoms. While the pathophysiology of microvascular angina is an ongoing topic of research, two of the major contributing factors appear to be endothelial-independent microvascular dysfunction and endothelial-dependent dysfunction [5]. This microvascular angina has been postulated to be more prevalent in women because of higher levels of inflammation and hormonal changes throughout women's lives. The higher prevalence of microvascular angina in women compared to men has led authors to address it primarily as a disease of women's hearts [35].

Microvascular Dysfunction

Microvascular dysfunction refers to disease in small coronary resistance vessels measuring 100–200 μm. It can encompass the abnormal coronary reactivity that is attributable to distal embolization from coronary plaque erosion, smaller arterial size, and positive remodeling [22, 29]. In the WISE study, one subset of 159 women with angina and non-obstructive CAD on coronary angiography underwent coronary flow reserve (CFR) testing. CFR was tested by injecting intracoronary adenosine and measuring the coronary velocity response. The CFR was found to be decreased in 47 % of these women, indicating disease of the microvasculature even in the absence of obstructive CAD [29]. Nuclear Magnetic Resonance Spectroscopy (NMRS) is a non-invasive imaging technique that uses a probe to detect different quantities of chemicals in a sample. Cardiac NMRS was also used in the WISE study to look for myocardial ischemia by measuring phosphocreatine/adenosine triphosphate ratio during handgrip exercise. Decrease in the phosphocreatine/adenosine triphosphate ratio in the heart signifies a shift from aerobic to anaerobic cellular metabolism, which indicates myocardial ischemia. In WISE, women with angina but no obstructive CAD, 20 % still showed evidence of myocardial ischemia on NMRS when performing handgrip exercise [8, 9, 36].

Retinal arteriolar narrowing is a noninvasive peripheral measure that can also be used to evaluate microvascular disease throughout the body [37]. In women with retinal arteriolar narrowing, there is an increased risk for development of IHD. In contrast, men with retinal arteriolar narrowing do not appear to have a significantly increased risk of developing IHD. Together, this combination of functional and pathological findings demonstrate that there are differences in the vasculature in men and women and suggests a significant role for the microvasculature in IHD. While obstructive CAD is established as the predominant pathology in men, microvascular disease appears to contribute disproportionately to the pathophysiology of heart disease in women.

Endothelial Dysfunction

Coronary endothelial function plays a role in regulating myocardial blood flow and can also be a predictor for future vascular disease. In the WISE study, investigators measured the change in coronary flow reserve in response to injections of acetylcholine (activating endothelial-dependent dilation), adenosine (non-endothelial-dependent microvascular dilation), and nitroglycerine (non-endothelial-dependent epicardial dilation) in women with angina but no obstructive CAD [38]. They identified that women with a poor response to acetylcholine had a higher rate of adverse IHD outcomes over a 4-year follow up. This suggests that endothelial dysfunction independently predicted and likely contributed to IHD. This warrants further research and may indicate a potentially new therapeutic target. In addition to invasive intracoronary injection of acetylcholine, brachial artery flow mediated dilation has been used as a peripheral measure of endothelial function and has also been correlated with increased IHD risk in women [5].

Risk Factors

Risk factors for microvascular dysfunction and endothelial dysfunction include many of the traditional risk factors associated with coronary atherosclerotic disease including obesity, dyslipidemia, hypertension, diabetes, and smoking. Increasing evidence also identifies psychological factors including stress and depression as having significant association with IHD and acute myocardial infarction [9, 39–42]. In women, and especially in post-menopausal women there is an increased clustering of many of the traditional risk factors for heart disease [5]. Additionally, vasculitis and general inflammatory auto-immune diseases such as lupus, rheumatoid arthritis, and thyroiditis have been associated with cardiac disease [14, 32]. Many autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have female predominance. Women with lupus in particular have been shown to have higher rates of cardiac disease beyond what would be estimated by their baseline traditional risk factors [43]. Accelerated atherosclerosis in patients with SLE and RA is associated with increased cardiovascular morbidity and

mortality [44]. Inflammatory conditions are also more prevalent in women and general rates of inflammation as reflected by elevated C-reactive protein have been shown to be elevated in women [14]. The combination of risk factor clustering, higher rates of depression, higher rates of vasculitis, and higher rates of general inflammatory conditions could offer some explanation for the disproportionate burden of heart disease and specifically higher rates of microvascular and endothelial dysfunction in women.

Hormonal Influence

Women also have an element of endothelial dysfunction that appears to correlate with hormonal changes throughout their lives and the lack of positive estrogenic effects on blood vessels after menopause [5, 42]. Estrogen has been identified as a likely factor contributing to the lower risk of IHD in premenopausal women compared to age matched male controls. After menopause, the reduction in estrogen appears to be accompanied by a decrease in its protective effects and an increase in the risk of IHD. Estrogen in the female heart appears to have a number of beneficial effects, which notably include improved endothelial function and decreased flow resistance as well as improved vascular response to injury. Experimental evidence points to increases in nitric oxide production and up regulation of nitric oxide genes as a mechanism by which estrogen improves vasodilation. Estrogenic effects on Estrogen Receptors (ER) alpha and ER beta in the vasculature appear to play a major beneficial role in flow resistance and vascular response to injury.

Microvascular angina encompassing endothelial-independent microvascular dysfunction and endothelial-dependent dysfunction is more prevalent in women than men. NHLBI-WISE also demonstrated that it portends a poorer prognosis in women independent of whether macrovascular dysfunction is present [22]. Additionally, in women with endothelial dysfunction there is also a significant association with increased cardiovascular events [5, 45]. Through optimal blood pressure control and improvement in the degree of measured endothelial dysfunction, some researchers have shown improvement in rates of IHD events [45, 46]. This both supports the major role of endothelial dysfunction in IHD and highlights blood pressure control as a target for improving IHD outcomes in women.

Figure 3.4 shows one proposed model for the pathophysiology of ischemic heart disease in women [5].

Spontaneous Coronary Artery Dissection (SCAD)

Spontaneous Coronary Artery Dissection (SCAD) is a phenomenon that includes spontaneous dissection of the coronary intima or media and intramural hematoma formation. SCAD does not include dissections caused by plaque dissection in coronary atherosclerosis, or trauma to the vessel wall during angiography. Rather, the

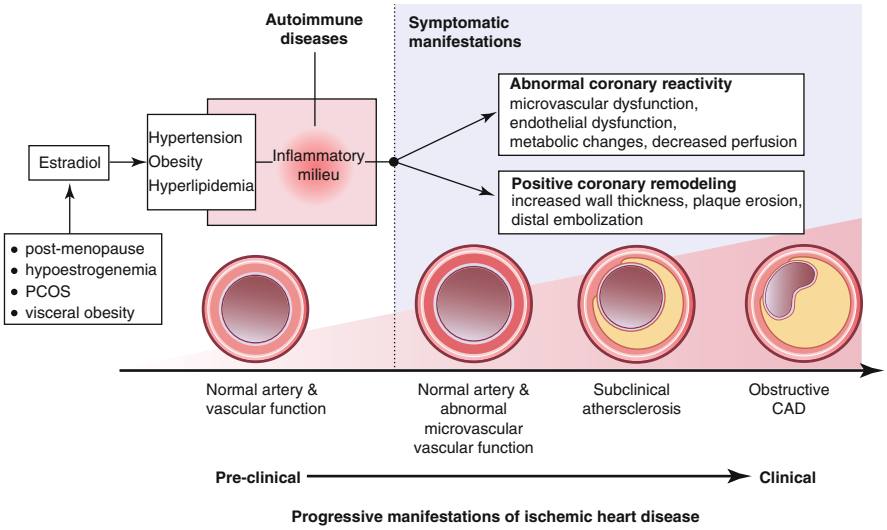

Fig. 3.4 One proposed model for the pathophysiology of ischemic heart disease in women (Reprinted from Shaw et al. [5] with permission from Elsevier)

current consensus is that SCAD is a separate entity that can occur in a heart without prior atherosclerotic disease [47–49]. SCAD continues to be an active area of research and has several unique features that make it especially applicable to a discussion of the female heart. The true prevalence of SCAD is not known, but has been estimated at 0.1–0.28 % of patients with ACS that undergo angiography or post-mortem examination. A recent cohort study estimated the overall annual incidence of SCAD as 0.26 per 100,000 persons. Despite this low overall incidence in the population, SCAD disproportionately affects women more than men (82 % vs. 18 %) and is associated strongly with peripartum status, which uniquely impacts the female heart.

Presentation of SCAD

On presentation, patients with SCAD commonly complain of chest pain and are often diagnosed with an acute coronary syndrome [47]. The presenting ACS diagnoses include 49 % STEMI, 44 % NSTEMI, and 7 % unstable angina. Ventricular tachycardia or fibrillation on presentation has also been recorded in 14 % of patients and multivessel coronary dissection in 23 %. The acute nature of SCAD and possible out of hospital mortality has led authors to believe that the presentation for a number of SCAD patients could be out of hospital sudden cardiac death. More widespread autopsy use in sudden cardiac death (especially in younger or peri-partum women) could reveal a greater incidence of SCAD in the population. Additionally, intraluminal hematoma formation without dissection is difficult to identify on angiography and could represent another area where SCAD is under diagnosed.

Diagnosis and Morphologic Characteristics of SCAD

There are several imaging techniques available that can diagnose SCAD including coronary angiography, intravascular ultrasound, and multidetector CT. The acute presentation of SCAD frequently leads patients to undergo coronary angiography. With contrast visualization, SCAD has been characterized as an: "involved lumen surrounded by a secondary, communicating lumen resembling a halo that fills and empties slowly; involved lumen longitudinally separated into two or three spaces by dissecting lines; or, coronary aneurysm that is seen to communicate, via a narrow neck, with the main lumen" [49]. Intramural hematoma can also develop and progress to obstruction of the coronary lumen, which can be visualized angiographically. Intravascular ultrasound further allows Doppler flow measurements to show flow into an intramural hematoma. Multidetector CT can noninvasively document SCAD and be used to follow change in the lesion(s) over time. Autopsy data, while limited in scope of practice, has helped to delineate the layers of coronary artery dissection.

The inciting factor and sequence of events for SCAD is not clear, and may vary from patient to patient. Spontaneous luminal dissection could result in hematoma formation or spontaneous hematoma formation could cause the dissection. Regardless of the inciting factor, both sequences of events can lead to extension and luminal obstruction that is clinically recognized as an acute coronary syndrome.

Figure 3.5 shows a coronary Angiogram of a 38 years old female presenting with chest pain and found to have a dissection/hematoma of the left coronary system (arrow).

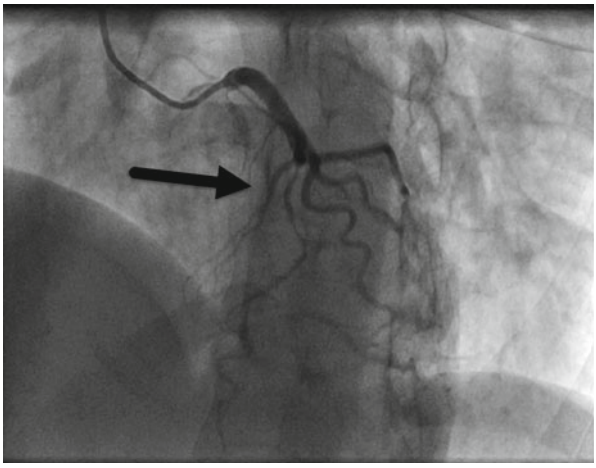

Fig. 3.5 Coronary Angiogram of a 38 years old female presenting with chest pain and found to have a dissection/hematoma of the left coronary system (*arrow*) (Image Courtesy of John Malzewski)

Predisposing Conditions for SCAD

Due to the low incidence, the total number of patients studied with SCAD is relatively small. Despite this, several interesting associations have been recognized including fibromuscular dysplasia, post-partum status, hormonal supplementation in women, and extreme physical activity in men [47]. SCAD has been indicated as the etiology of peripartum ACS in 16 % of patients. The change in hormonal status both in the post-partum patient and patient undergoing hormone supplementation might suggest that there is a role for alterations in the vasculature during these times which predisposes to SCAD. Fibromuscular dysplasia, which has been identified in 50 % of patients with SCAD, could be another predisposing factor which, under the right circumstances, can lead to SCAD. Extreme physical activity (more commonly seen in men than women with SCAD) could represent an inciting stress on an already predisposed vessel. While a single unifying genetic, hormonal, or environmental cause has not yet been identified in all patients with SCAD, it is not unreasonable to approach it as a combination of multiple underlying predisposing factors manifesting in the right environment.

Management and Prognosis of SCAD

Management of SCAD has not yet been studied with randomized controlled trials, and it would be very difficult to do so given the low incidence of the disease. Cohort studies and case reports give some data on outcomes with various interventions [47, 50], but because of their selection bias, have to be interpreted with caution. In a cohort of patients presenting with ACS and found to have SCAD on angiography, conservative management without intervention generally has resulted in the best outcomes with little acute in-hospital complications. Percutaneous coronary interventions are frequently much less successful in SCAD (65 % of patients) than in plaque mediated ACS and were frequently more complicated by failure to cross the lesion or propagation of the lesion leading to worse TIMI flow after the procedure. CABG has been seen as initially successful, but in one cohort 73 % of grafts that were placed were found to be occluded on follow up. While this data cannot definitively indicate a single best approach, it importantly highlights the high complication rate and risk of harm with interventions for SCAD compared with the same interventions when utilized for plaque mediated ACS.

Prognosis for patients after an initial SCAD event regardless of intervention appears to be better than that for other patients with ACS, with 1-year mortality estimated at 1.1 % and 10 years mortality estimated at 7.7 %. The recurrence rate however is high with 17 % at 4 years and 29 % at 10 years. Patients with SCAD reportedly have less hyperlipidemia, hypertension, tobacco abuse, and diabetes mellitus. However, due in part to the high rate of recurrence, the overall 10 years survival free from the combined endpoints of death, recurrent SCAD, myocardial infarction, or congestive heart failure is similar to other patients presenting with ACS [47].

Summary

Ischemic heart disease affects millions of American men and women. The gender paradox of increased ischemic heart disease burden in women despite decreased prevalence of obstructive CAD has led us to recognize that there is a variety of underlying pathophysiology that leads to ischemic heart disease. Obstruction in blood flow through the large epicardial coronary arteries through the process of atherosclerosis is recognized as the most common cause of ischemia in both male and female hearts. Dysfunction in the microvasculature through both endothelial independent microvascular disease and endothelial dependent disease is being increasingly recognized and is notable for its greater prevalence in the female heart. Hormonal, inflammatory, and anatomic differences between the genders likely impact the different prevalence of epicardial and microvascular disease between men and women and continue to be active areas of research. The prevalence of various symptoms of ischemic heart disease also differs between men and women. Many symptoms previously described as "atypical" are now understood to be part of the normal spectrum of IHD symptoms in women and should warrant appropriate evaluation for ischemic heart disease. The difference in underlying pathology between many male and female hearts may play a role in the difference in symptom presentation. Lastly, spontaneous coronary artery dissection, while an infrequent cause of acute coronary syndrome, is notable for its predilection for younger female hearts without traditional risk factors or presence of atherosclerosis. With research revealing more about the hormonal, inflammatory, and anatomic differences in male and female hearts, strategies for diagnosing and managing ischemic heart disease are increasingly tailored with respect to gender.

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