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Characteristic Symptoms in Women with Ischemic Heart Disease

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Published online: 2 May 2019
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Abstract

Purpose of Review Advances in coronary imaging techniques have revealed that there are important sex differences in the pattern of ischemic heart disease. In this review, we aim to summarize our current knowledge and focus on the relation between a distinct symptom presentation in women and their underlying type of coronary artery disease.

Recent Findings Women in the age group 40–70 years more often have non-obstructive coronary artery disease (CAD) and coronary vasomotor disorders compared with the traditional obstructive CAD as seen in men. These differences in pathophysiology translate into another symptom presentation which we should rather call characteristic than atypical. Women at risk for coronary vasomotor disorders often have co-morbidities and an enhanced pro-inflammatory state, which leads the way to the appropriate diagnosis. Progress has been made with invasive testing to better discriminate between coronary spasm and microvascular dysfunction. Treatment options are still limited and often disappointing for this heterogeneous patient population.

Summary Sex differences in ischemic heart disease truly exist and have been clearly defined over the past years. We should therefore approach female patients according to this acquired knowledge. The challenge for the coming years will be a more tailored diagnostic and therapeutic approach for symptomatic women at middle-age.

Keywords Atherosclerosis · Coronary spasm · Ischemic heart disease · Microvascular dysfunction · Women

Introduction

Female patients have historically been confusing for cardiologists. Being educated in treating obstructive coronary artery disease (CAD), its different pattern of symptoms and atherosclerosis have surprised so many. In the early 1990s of the last century, it was first assumed that women were discriminated in diagnostics and treatment of CAD [1, 2]. In addition, it was considered that gender issues in CAD were mainly driven by a different way in symptom expression and not by biological (sex) differences.

With the evolving knowledge gained by many percutaneous coronary intervention (PCI) research programs for acute coronary syndrome (ACS) and elective PCI over the past decades, we have learned that sex differences in

ischemic heart disease (IHD) truly exist. Obstructive CAD occurs 7–10 years later in women than in men, and women have fewer focal stenotic lesions at all ages [3]. They have a lower plaque burden with less vascular calcifications, a more diffuse pattern of atherosclerosis, and more often soft plaques and erosive lesions [4–7]. Only a quarter of all included patients in PCI registries are women, reflecting their different pattern of disease [8•]. When having an ACS or an elective PCI, women are older with a higher clustering of traditional CVD risk factors. Coronary vasomotor disorders, such as coronary artery spasm (CAS) and endothelial dysfunction, represent a major cause of ischemic cardiac symptoms in middle-aged women.

Differences in underlying pathophysiology lead to a more distinct presentation of angina symptoms and warrant a more gender-sensitive, diagnostic, and therapeutic approach than the usual male-oriented pathway. As appropriate diagnoses are often lacking, this leads to an ongoing under-treatment and results in adverse outcomes in the long run. It is therefore not amazing that we observe a rise in the number of hospitalizations for ACS in younger women, even under 55 years of age [9•, 10•].

This article is part of the Topical Collection on *Women and Heart Disease*

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Ischemia with Non-obstructive Coronary Arteries

Women with symptoms of angina have twice as often ischemia with non-obstructive coronary arteries (INOCA) compared with men [3, 11]. Another often used term is NOCAD, meaning non-obstructive coronary artery disease. The over-emphasis of obstructive CAD over INOCA in our guidelines is one of the main reasons that women are still less well treated than men [12]. When coronary stenosis is less than 50% at angiography, with a fractional flow reserve (FFR) ≥ 0.80 , it is considered to be not significant. Non-obstructive CAD is often present in combination with coronary vasomotor disorders, such as spasm and endothelial dysfunction of the larger and smaller branches of the coronary tree [13, 14]. In most symptomatic patients, intravascular ultrasound (IVUS) shows some signs of coronary atherosclerosis [15]. However, IVUS is not routinely carried out in patients with INOCA, which may lead to the misdiagnosis of “clean arteries” and subsequent undertreatment of symptoms and risk factors. It has been demonstrated that INOCA is not a benign condition and that it has a higher 5-year event rate in symptomatic women compared with men, especially when signs of ischemia are present [16, 17]. Women with INOCA represent a very heterogeneous group, regarding the extent of atherosclerosis, the presence of risk factors, symptoms, and functional impairment.

Fluctuating Symptoms in Women with INOCA

The clinical evaluation of symptoms of angina pectoris in women is still considered along with the male standard of obstructive CAD. The combination of INOCA with vasomotor disorders frequently occurs in young and middle-aged women. Whereas typical symptoms of angina are more related to epicardial stenoses, the combination of INOCA with vasomotor dysfunction has other characteristics. Depending on the involvement of coronary spasm and endothelial dysfunction, chest pain may occur both at rest and during exercise and often varies over time. Symptoms fluctuate within days and weeks and may present in a crescendo/decrescendo pattern. The majority of patients feel unusually tired with a lack of energy. The traditional risk factors such as hypertension and dyslipidemia may serve as triggers for vascular dysfunction and coronary spasm. Stress-related factors are equally important risk factors and can also act as triggers for vascular dysfunction [18, 19, 20]. Stressful circumstances and events often aggravate the duration and intensity of symptoms [21].

Lack of patient awareness and gender differences in communication styles frequently hamper the early recognition of angina in women. In addition, women’s communication is more likely to be emotional, subjective, polite, and self-revealing with more concern and awareness for the feelings

of others. Men usually report their symptoms in a direct way, while female patients ask more questions, present more and diverse symptoms, and give more detailed histories of their activities. This can be misleading to both female patients and their doctors for the correct interpretation of their cardiac symptoms. The diverse symptoms of stable angina in women are depicted in Table 1.

Coronary Microvascular Dysfunction Type 1 Dominates in Women

In more than 60% of patients with INOCA, there is concomitant involvement of coronary microvascular dysfunction (CMD) [22, 23]. Functional and/or structural abnormalities in the coronary microcirculation result in impaired vasodilatation (endothelium-dependent and endothelium-independent mechanisms) and an increased vasoconstriction level caused by various stimuli [24, 25]. Type 1 CMD with functional impairment typically occurs in women between 40 and 70 years of age and is characterized by the absence of obstructive CAD or other structural heart diseases. Important contributing factors are obesity, smoking, and traditional cardiovascular risk factors (dyslipidemia, hypertension, diabetes). In addition, an enhanced inflammatory state such as in rheumatic diseases and chronic intestinal bowel syndromes also predispose for CMD [26, 27]. It is increasingly acknowledged that small vessel damage in the heart is a systemic phenomenon and that these patients have generalized endothelial dysfunction leading to abnormal vascular reactivity [25, 28]. An enhanced inflammatory state with signs of premature vascular dysfunction may also be the reason that patients with type 1 CMD relatively frequently report a previous history of migraine and severe hypertensive pregnancy disorders [29, 30]. We have recently shown that women after preeclamptic pregnancies have a twofold higher risk for identifiable coronary calcium with CT (CAC score) compared with women after normotensive pregnancies [31]. It is therefore essential to ask for these life events and co-morbidities when considering the diagnosis type 1 CMD (Fig. 1) [32].

Symptoms in patients with type 1 CMD overlap strongly with INOCA and share their fluctuating and often unpredictable character. Angina pectoris can occur both during exercise and spontaneous in the evening or at night. Affected patients often report to be extremely tired in the days after many activities.

Diagnosis and Management of Coronary Vasomotor Disorders

The Coronary Vasomotion Disorders International Study Group (COVADIS) has recently published two separate consensus statements on vasospastic angina and microvascular

Table 1 Classification of angina with female-specific aspects (♀)

Typical angina (definite)	Meets 3 of the following characteristics: <ul style="list-style-type: none"> • Oppressive substernal chest discomfort • Provoked by exertion or emotional stress • Relieved by rest and/or nitrates within minutes ♀ Squeezing, tight, chest discomfort ♀ Radiation to chest, jaw(s), left armpit and/or left arm, neck, shoulders, and inter-scapular area ♀ May last longer than minutes ♀ Crescendo /decrecendo character (spasm) ♀ Dyspnea, anxiety, mental stress-related ♀ Extreme tiredness, also often after angina episode
Atypical angina (probable)	Meets 2 criteria ♀ Both typical and atypical symptoms in NOCAD
Non-anginal chest pain	Lacks or meets only one characteristic criterion ♀ Beware of cardiac anxiety disorder

Adapted from: Montalescot G et al., 2013 ESC guidelines stable CAD

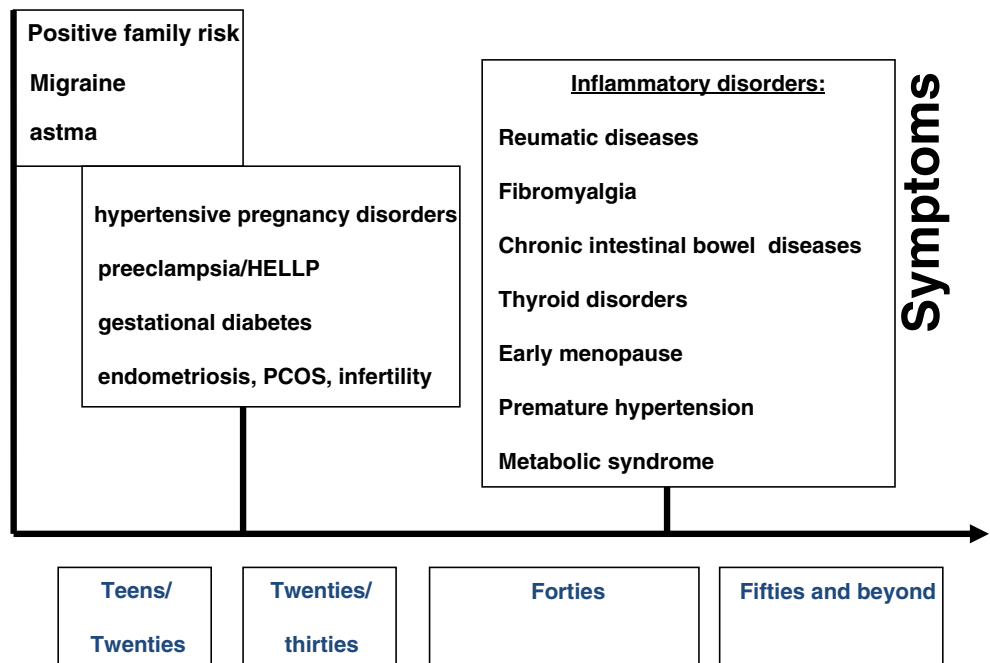
angina as guidance for coronary vasomotor disorders [33, 34••]. As the diagnosis cannot be established based on symptoms alone, additional non-invasive and invasive testing for ischemia are recommended. With positron emission tomography (PET) using ammonia, coronary flow reserve (CFR) can be measured. A CFR < 2.5 is considered to be abnormal and a CFR < 2.0 is associated with adverse cardiac outcomes [35]. Despite, in many symptomatic patients, PET scans are not abnormal, presumably because vasospastic angina dominates over CMD.

Obstructive CAD can be ruled out with CT angiography when a coronary angiography has not been done previously. The best way to establish the diagnosis of vasomotor disorders is to perform invasive measures of the index of microvascular resistance

(IMR) and CFR and to perform vasoreactivity testing with acetylcholine. This can be safely done by expert invasive cardiologists, using a standardized protocol [36, 37]. These invasive tests are important to discriminate between vasospasm of the epicardial coronary arteries and the coronary microvasculature. Abnormal test results are associated with adverse outcomes [38].

Treatment of coronary vasomotor disorders starts with lifestyle interventions and appropriate and adequate control of the traditional risk factors. The use of anti-platelet therapy is not routinely recommended, whereas statins are primarily indicated when lipid levels are elevated. Importantly, blood pressure should be more strictly treated than what the guidelines advice. In most patients, short-acting nitrates are helpful to

Fig. 1 Life course approach in women with angina pectoris at middle-age



relieve symptoms, but not at all times [12, 39]. Long-acting nitrates may even aggravate symptoms. Depending on the resting heart rate, high doses of calcium-antagonists can be given, preferably diltiazem, even combined with low doses selective beta-blockers. In patients with refractory angina, non-traditional treatment options can be beneficial. These include xanthine derivatives, ivabradine, nicorandil, and ranolazine [12, 39, 40]. The use of postmenopausal hormone replacement therapy has no additional beneficial effect in women with CMD. As there is no standard treatment suited for every patient, it may take time to find the best individual options. Stress reduction programs with mindfulness and yoga can be helpful in symptom reduction.

Conclusion

Advances in coronary imaging and the increased attention to coronary vasomotor disorders over the past years are important reasons why female patients are now more into the spotlight. Progress has been made in better defining their characteristic symptoms with important diagnostic and therapeutic steps forward. However, many questions are still unresolved. More fine-tuning in diagnosis and therapy is needed to better serve each individual patient.

Compliance with Ethical Standards

Conflict of Interest The author declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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