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How to decipher the mystery of a woman's heart? A practical guide.

I Frederix, E Govaerts and P Dendale provide a practical guide on how to approach a woman with presumed ischemic heart disease (IHD).

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Women remain underrepresented in most of current research on cardiovascular disease. This is despite the established presence of important gender differences for the majority of cardiac pathologies. Concurrently, the cardiovascular disease burden in middle-aged women is increasing relatively to men. This calls for action! The objective of this report is to provide the reader with a practical guide on how to approach a woman with presumed ischemic heart disease (IHD). Furthermore, it serves as a means to increase awareness for the female heart and to promote research exploring the fundamental biological differences that exist between men and women having an impact on the epidemiology, pathophysiology, diagnosis and/or treatment of cardiovascular disease.

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Topic(s): Epidemiology, Prevention

Epidemiology

According to the old myth, IHD was perceived as a disease predominantly affecting males, rooted in the belief that women are protected against cardiovascular disease. The reality however, is somewhat different. Both genders are about equally affected. With 21% of females and 20% of males dying from IHD, it is the main cause of death across Europe (1,2). Moreover, recent data show that while the prevalence and mortality of IHD is declining in men, this is not the case for women (3). Although female patients tend to have less anatomical obstructive coronary artery disease; they suffer from greater mortality rates compared with similarly aged men (i.e. the paradoxical gender difference) (4). Unfortunately, despite substantial efforts over the last decades to educate medical caregivers about the risk of IHD in women; differences in attention for and recognition of this subtype of cardiovascular disease across genders persist.

Cardiovascular risk factors

As indicated by the "higher risk factor burden hypothesis", female patients appear to acquire a heavier load of traditional cardiovascular risk factors then men before establishing IHD (5). Once IHD has developed, women tend to have an increased number of risk factors, when compared to age-matched male patients. Demographically, women have a higher load of cholesterol levels than men after their 5th decade of life, their HDL-cholesterol decreases mildly after menopause (6,7). Hormonally-mediated metabolic disturbances after menopause are furthermore held responsible for the clustering of risk factors (arterial hypertension, obesity and hyperlipidemia) at this stage of life.

In EUROASPIRE IV, males were more likely to be smokers than women (8). However, also in women smoking is associated with an increased risk for all-cause mortality, non-fatal infarction and unstable angina (9).

While the traditional risk factors typically underestimate the IHD risk in women, newly established risk factors are emerging and ameliorating risk detection (4). As such, it has been observed that women on average have greater mean C-reactive protein (CRP) levels compared to men; suggesting a possible role for inflammation in IHD sex differences. It was hypothesized that high inflammatory marker levels act synergistically with other traditional risk factors to speed up the development of IHD in women. Increasing concentrations of high-sensitivity CRP (hsCRP) have been positively correlated with the risk of future IHD events.

The role of female hormones in the pathophysiology of IHD has been debated for years. Estrogens were confirmed to regulate several metabolic factors such as lipids, the coagulation system and inflammatory markers. They have a nitric oxide mediated vasodilation effect on the vessel wall; which was supposed to be cardioprotective (10). Paradoxically, postmenopausal hormonal replacement therapy was shown to increase the risk for cardiovascular disease. The reason for this "hormonal paradox" is not completely elucidated. The fact that healthy endothelium is estrogen responsive whereas endothelium damaged by atherosclerosis is not, provides one plausible explanation. Recent analyses of the Women's Health Initiative data do not provide justification for the use of postmenopausal hormone therapy for the prevention of cardiovascular disease, but support use in young symptomatic women without adverse risk factor profiles for a short period (11).

Traditional risk factor scoring systems

As traditional cardiovascular risk factor scoring systems typically underestimate individual female patient risk, novel sex-specific tools have been devised (12). The Reynolds risk score as an example, reclassifies the cardiovascular risk in >40% of intermediate risk women compared with traditional risk factor scoring systems. It uses the following equation: 0.0799 x age + 3.137 x natural logarithm (systolic blood pressure) + 0.180 x natural logarithm (hsCRP) + 1.382 x natural logarithm (total cholesterol) −1.172 x natural logarithm (high-density lipoprotein cholesterol) + 0.134 x hemoglobin A1c (%) (if diabetic) + 0.818 (if current smoker) + 0.438 (if family history of premature MI).

Pathophysiology

Contrary to male patients, women less frequently present with obstructive and extensive epicardial artery disease; they predominantly suffer from coronary plaque erosion and distal embolization. Abnormal coronary microcirculation, thrombophilia and non-atherosclerotic coronary artery dissection account more often to ischemic symptoms in women (13,14). The lifelong influence of varying reproductive hormone levels related to ovarian cycling, pregnancy and menopause were also identified as related to vascular function in the healthy and pathological cases (4). Brachial artery flow-mediated dilation is impaired in dyslipidemic, hypertensive, smoking and diabetic women, indicating the possible pathophysiological role of endothelial (dys)function in IHD.

Clinical presentation

Timely recognition of ischemic symptoms in women is paramount. Failure to do this can result in delays in correct diagnosis and treatment, negatively impacting the patient's long-term prognosis. Prior observational studies suggested gender differences in ischemic symptoms, some of this due to women presenting at older ages and symptoms becoming less specific with advancing age (15). Mackay et al. however, did not reproduce these observations in their prospective research on intentionally transient reduced regional coronary blood flow (16). They reported no significant differences between men and women in the prevalence of reporting chest pain or most other typical symptoms during ischemia. Women did perceive chest pain earlier after the onset of ischemia, and more often reported throat and jaw discomfort compared to men. Similar findings were concluded in the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), exploring gender differences in the presentation of IHD in 10,003 symptomatic patients (17). Measures to ensure medical caregivers are alert for the classic clinical presentation of myocardial ischemia also in women, may be warranted.

Diagnosis

Clinicians preferably select imaging stress tests (stress echocardiography or nuclear stress testing) for women when compared to men, with a clear rationale (17). Exercise ECG's are found to have a lower sensitivity and specificity for detection of obstructive IHD in women. The nonspecific endogenous estrogen induced resting ECG changes mimicking ischemia and the lower exercise capacity are contributing to this phenomenon (13). The lower obstructive IHD prevalence provides another explanation.

In contrast, stress echocardiography is of added value in women to assess stress-induced wall motion abnormalities. It successfully discriminates stable angina caused by epicardial artery stenosis from microvascular angina. Angina and ischemic ST changes in the absence of regional wall motion abnormalities are a hallmark of the microvascular origin of myocardial ischemia.

Coronary angiography, although the golden standard to detect obstructive coronary artery disease, may be less suited in women. Particularly younger and middle-aged women more often present with ischemic symptoms due to aberrant coronary vascular reactivity and microvascular abnormalities in the absence of epicardial artery stenoses. However, as shown in the WISE (NHLBI-sponsored Women's Ischemia Syndrome Evaluation) study, symptomatic women without angiographically obstructive coronary arteries had a twofold elevated major adverse event rate (cardiovascular death or myocardial infarction) (18), compared to asymptomatic community control women. It follows that "negative" coronary angiographies do not equate to normal coronary arteries in women.

Treatment

Secondary prevention of IHD by means of cardiac rehabilitation (CR) is proven effective to reduce subsequent myocardial infarctions, recurrent hospitalizations, and mortality (19). Gender differences in CR referral and attendance were recently explored in a retrospective cohort study (N = 25,958), based on the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) and Cardiac Wellness Institute of Calgary (CWIC) databases (20). Female sex was associated with reduced rates of both referral to and attendance of CR, despite the fact that the women who were not referred to CR had the highest mortality of all subjects (higher relative to men who were not referred).

The gender gap in risk factor control of patients with IHD was further examined as part of the EUROASPIRE IV (EUROpean Action on Secondary and Primary Prevention through Intervention to Reduce Events) survey; a cross-sectional survey including centers from 24 European countries (8). Female patients had a worse risk factor profile, males were more likely to have a LDL-cholesterol on target, to be non-obese, and to perform adequate physical activity. Anxiety and depression, known risk factors for adverse cardiac outcomes and mortality (21, 22), were more prevalent in women. Cardiovascular drug use for secondary prevention of IHD, was reported in the PHARMO trial (23). Female patients were less likely to use antitrombotic drugs, a similar trend was seen for lipid-lowering drugs.

Conclusion & take home messages

This paper provides the reader with a practical guide on how to decipher the mystery of the female ischemic heart. Contrary to old myths, IHD also affects women and is identified as a major cause of mortality. Novel risk factors are emerging to enhance risk assessment with the traditional cardiovascular risk factors. Microvascular and endothelial dysfunction more often contribute to ischemic symptoms in female patients, as contrasted to obstructed epicardial coronary arteries in men. Non-invasive imaging stress tests are valuable diagnostic tools especially in female, given the lower sensitivity and/or specificity of exercise ECG's and coronary angiographies when compared to men. Greater emphasis needs to be placed on improving referral to and attendance of CR for women, positively impacting their quality of care and further decreasing mortality (24).

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