Atherosclerosis 239 (2015) 260–267

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Sex differences in coronary artery disease: Pathological observations

Kazuyuki Yahagi [a], Harry R. Davis [a], Eloisa Arbustini [b], Renu Virmani [a, *]

[a] CVPath Institute, Gaithersburg, MD, USA
[b] Center for Inherited Cardiovascular Diseases, IRCCS Foundation Policlinico San Matteo, Pavia, Italy

ARTICLE INFO

Article history:
Received 4 November 2014
Received in revised form
30 December 2014
Accepted 14 January 2015
Available online 20 January 2015

Keywords:
Sex differences
Atherosclerosis
Coronary artery disease
Plaque erosion
Menopause
Smoking

ABSTRACT

Cardiovascular disease (CVD) remains the most frequent cause of death in both men and women. Many studies on CVD have included mostly men, and the knowledge about coronary artery disease (CAD) in women has largely been extrapolated from studies primarily focused on men. The influence of various risk factors is different between men and women; untoward effects of smoking of CAD are greater in women than men. Furthermore, the effect of the menopause is important in women, with higher incidence of plaque erosion in young women versus greater incidence of plaque rupture in older women. This review focuses on differences in plaque morphology in men and women presenting with sudden coronary death and acute myocardial infarction.

Cardiovascular disease (CVD) remains the most common cause of death in both men and women, despite the introduction of new modalities for its treatment. In 2009, 386,436 men and 401,495 women died of cardiovascular disease in the United States [1]; women represented 51.0% of deaths from CVD. In 2012, CVD accounted for 17.3 million deaths/year worldwide however, this number is expected to grow to more than 23.6 million by 2030 [2] because of increasing obesity, which has doubled between 1980 and 2008, and is expected to further increase.

Many studies on CVD have included mostly men, and the knowledge about coronary artery disease in women has largely been extrapolated from studies primarily focused on men. Therefore, it is not surprising that there has been an underestimation of the importance of cardiovascular disease in women for many years. In 1998 it was published that the cause of death from cardiovascular disease in women was nearly twice that from cancer, these statistics have not changed much since then [3]. Also, we know in 2013 that the rate of awareness of heart disease as a leading killer of women was twice than in 1997 (56% vs. 30%); however, more improvement is needed especially among minorities and underprivileged sections of the population [4].

Lifetime risk of overall CVD approaches 50% for persons aged 30 years without known CVD [5]. Coronary heart disease (CHD) accounts for approximately one-third to one-half of the total cases of CVD. The lifetime risk of CHD is well illustrated in the Framingham Heart Study of 7733 participants, age 40 to 94, who were initially free of CHD. Lifetime risk of coronary heart disease at age 40 years was 48.6% (95% CI 45.8–51.3) for men and 31.7% (29.2–34.2) for women. At age 70 years, lifetime risk was 34.9% (31.2–38.7) for men and 24.2% (21.4–27.0) for women [6].

1. Nonatherosclerotic coronary artery disease

Although a large prevalence of CVD in women is associated with coronary atherosclerosis, less common causes of acute coronary syndromes in women include spontaneous coronary dissections (SCAD), Takayasu's syndrome, and Takotsubo cardiomyopathy [7]. Takayasu's syndrome typically occurs in young women, which is predominantly associated with aortitis involving the aorta and its main branches, however coronary arteries may be less frequently involved; other rare causes include cocaine vasculitis and myocardial bridging.

A coronary dissection is a clinically neglected cause of acute myocardial ischemia. About 70% of coronary dissection cases reported to date occurred in women [8]. Recently SCAD has been associated with fibromuscular dysplasia (FMD), however most cases of FMD are associated with renal arteries followed by carotid

* Corresponding author. CVPath Institute, Inc., 19 Firstfield Road, Gaithersburg, MD 20878, USA.
E-mail address: rvirmani@cvpath.org (R. Virmani).

http://dx.doi.org/10.1016/j.atherosclerosis.2015.01.017
0021-9150/

and vertebral arteries. In a recent publication involving 177 women, less than 50 years in age, undergoing coronary angiography, 42.9% presented with acute coronary syndrome (ACS) and 57.1% had stable symptom or atypical chest pain. Ninety-seven (55%) had normal arteries, 54 (31%) had atherosclerotic coronary artery disease (ACAD), 23 (13%) had nonatherosclerotic coronary artery disease (NACAD), and 3 (2%) had unclear etiology. Of the 23 NACAD, SCAD was observed in 16 (70%), all were troponin-positive and 13 of the 16 had noncoronary FMD, and 2 had irregular beading of coronary arteries suggestive of FMD. Of the 66 who presented with myocardial infarction, 24 (36%) had ACAD, 20 (30%) had NACAD, 19 (29%) had normal arteries (3 Takotsubo cardiomyopathy), and in the remaining 3 the etiology was unclear [9].

Coronary vasospasm that is a sudden occlusive or subocclusive vasoconstriction of an epicardial coronary artery and the primary cause of variant, or Prinzmetal, angina occurs more frequently in women. Takotsubo Cardiomyopathy is a gender-specific cause of transient acute ischemic heart disease; although coronary microvascular dysfunction, coronary spasm, catecholamine toxicity and myocarditis have been suggested to contribute to the occurrence of Takotsubo cardiomyopathy, the pathophysiology and the pathologic substrates are still far from completely elucidated. Pregnancy-related cases of Takotsubo cardiomyopathy have been reported to occur frequently after cesarean sections and the clinical presentation can mimic ACS [10].

2. Atherosclerotic coronary artery disease

2.1. Risk factors

Most of the risk factors for coronary artery disease (CAD) are similar for men and women. These may be divided into modifiable risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, physical inactivity, obesity and diet, whereas the non-modifiable are age, gender, and family history. However, the role of menopause is unique to women. CAD is unusual in premenopausal women, particularly in the absence of other risk factors [11]. On the other hand, the postmenopausal state as risk factor for CAD in women is similar to men [12] and the incidence of MI in women markedly increases after the menopause [11]. The increase is at least in part due to increasing age, since men also have a progressive increase in MI with age [11]. Hormonal status is also known to influence CAD risk in men, because men with the common genetic variation in estrogen receptor alpha (homozygous) have 3.0-fold greater odds of MI (95% CI, 1.7–5.2; P < 0.001) as compared to those without variant [13].

Burke AP et al. assessed the risk factors associated with morphologic characteristics of culprit plaques in 51 women with coronary heart disease and sudden death and compared to women dying of other causes (controls) (Table 1) [14]. We have observed that the risk factors associated with erosion are different from those associated with rupture, women dying with plaque rupture had higher TC, but HDL was not different as compared to controls where as for plaque erosion, smoking was only risk factor [15,16]. Consistently, smoking has been associated with acute thrombosis in pathologic and clinical studies, irrespective of gender. Women who smoke are more likely to have myocardial infarction than men who smoke [17]. Further, levels of TC correlated with an increase in the number of thin-cap fibroatheroma, which are significantly more frequently observed in women with plaque rupture [18].

The Women's Ischemia syndrome Evaluation (WISE) an NHLBI funded project was a prospective cohort study of women 18 years or older (n = 936, mean age 58 ± 12 years) who were undergoing a clinically indicated coronary angiogram for chest pain symptoms, myocardial ischemia and downstream major adverse clinical events. This study showed that persistent chest pain (PChP) at 1-year amongst the entire cohort was high (45%) and was similar to those with no obstructive CAD (46%). Those without obstructive CAD, but PChP had more than twice the rate of adverse CVD events (p = 0.03) that includes non-fatal MI, stroke, heart failure, and CVD-related deaths, compared to those without PChP [19].

A study in Finland showed that the incidence of CHD in men compared with women was approximately 3 times higher and mortality was approximately 5 times higher. Most of the risk factors were more favorable in women, but the sex difference in risk factor levels diminished with increasing age. Differences in risk factors between sexes, particularly in HDL/total cholesterol ratio and smoking, explained nearly half of the difference in CHD risk between men and women. Differences in serum total cholesterol level (TC), blood pressure, body mass index (BMI), and diabetes prevalence explained about one-third of the age-related increase in CHD risk among men and 50%–60% among women [20].

Cholesterol profiles of men and women differ with age. Levels of low-density lipoproteins (LDL) are lower in women than in men until the age of 50, when LDL levels increase in women. In women of all ages, high-density lipoproteins (HDL) are about 10 mg/dl higher than in men. In perimenopausal women, levels of lipoprotein (a) increase with age. This change in lipid levels may help explain the increase of CAD in older women. Epidemiologic studies have confirmed that high cholesterol is a risk factor for CAD in women. Low HDL is more predictive of coronary risk in women compared to men [21]. Furthermore, the relative predictive value of the different lipid parameters were evaluated in the Women's Health Study of 15,632 US women, initially healthy aged 45 years or older (interquartile range, 48–59 years) followed over a 10-year period for the occurrence of future cardiovascular events. The ratio of total cholesterol to HDL-C (HR 3.81 [95% CI, 2.47–5.86]) was highly predictive of further cardiovascular events in women [22].

Diabetes mellitus is an important predictor of CHD risk in men and women. Framingham Study suggested that diabetes is a more significant coronary risk factor for women than men [23]. Moreover, a meta-analysis of 37 studies involving 447,064 patients with type 2 diabetes showed that the overall relative risk for fatal CHD in women with diabetes was 3.5 whereas for men it was 2.1 [24].

Systolic blood pressure and isolated systolic hypertension are major CHD risk factors at all ages and in both genders [25]. The Framingham study found that there was a gradual shift from diastolic blood pressure to systolic blood pressure and then to pulse pressure as predictors of CHD risk with increasing age [26]. In patients <50 years of age, diastolic blood pressure was the strongest predictor of CHD risk. Age 50–59 years was a transition period when all 3 BP indexes were comparable predictors, and from 60 years of age on, diastolic blood pressure was negatively related to CHD risk so that pulse pressure became superior to systolic blood

Table 1
Multivariate association between risk factors and morphologic characteristics of culprit plaque in 51 women compared with 47 noncoronary deaths (trauma and cardiac noncoronary).

Risk factor	Plaque morphology	P value (univariate)	Multivariate		
			z score	P value	Odds ratio
Total cholesterol (mg/dL)	Rupture	<.0001	3.0	0.002	31
Cigarette smoking	Erosion	0.003	2.5	0.01	16
Glycosylated hemoglobin >8%	Stable plaque	0.001	2.8	0.006	7.1
Hypertension	Stable plaque	0.006	2.3	0.02	4.0

(Reproduced with permission from Burke AP et al., Am Heart J 2001; 141: S58-62).