Characterization and identification of women with angina pectoris

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Introduction

In the last few years there has developed an increasing interest in and awareness of the importance of sex differences in the epidemiology, presentation, identification and management of coronary artery disease. Not surprisingly, the apparent gender bias against women with respect to the use of resources, in the form of referral for further investigation, coronary angiography and revascularization[1] has generated considerable publicity. The likening of this phenomenon to the Yentl syndrome in an editorial by Bernadine Healy, then Director of the National Institutes of Health, has been widely quoted[2] and steps have been taken to redress the balance[3,4]. Rather than reiterate the differences in management of men and women with suspected or documented coronary artery disease the purpose of this review is to characterize women with chest pain and to distinguish those patients with cardiac pain from those with non-cardiac symptoms. An understanding of the differing modes of presentation of men and women with coronary artery disease and how risk factors for heart disease are influenced by gender, together with an appreciation of the role of non-invasive and invasive tests in the assessment of patients with chest pain, will enable the attending physician to maximise his or her chances of establishing the correct diagnosis and managing the patient appropriately.

Differing presentations of heart disease in men and women — the Framingham perspective

The Framingham study, which began in 1948, is a longitudinal prospective study of cardiovascular disease involving several thousand men and women. In 1972 the natural history of angina pectoris was reported and several sex differences emerged[5]. Compared with men angina was the most common presentation of coronary artery disease in women (65% vs 37% in men) although the clinical course was less complicated. Subsequent myocardial infarction was twice as likely in men with angina compared with women. The 26-year follow-up of the Framingham population, reported in 1996[6], demonstrated that the incidence of angina pectoris increased in men with age, peaking between 55 and 65 years and then declining in older men. In contrast, the rate in women increased in parallel with men until 55 to 65 years, when it continued to rise, making angina a predominantly female disease over the age of 75 years.

The most recent Framingham report, published in 1993[7], focused on gender differences in prognosis after the onset of coronary artery disease. Women were more likely to present with angina (47%) then either recognised myocardial infarction (18%) or unrecognised myocardial infarction (14%), unstable angina (7%) or death due to coronary artery disease (14%). In contrast, myocardial infarction (recognised and unrecognised) accounted for nearly half of first presentations in men (46%), followed by angina (32%), death (16%) and unstable angina (6%).

The mean age at onset of angina was greater in women than in men (64 years vs 61 years) and women generally had a worse risk factor profile, with higher plasma cholesterol levels (6-71 mmol. l⁻¹ vs 6-19 mmol. l⁻¹ in men), a higher incidence of diabetes mellitus (12% vs 10%) and hypertension (49% vs 35%) but a lower incidence of smoking (22% vs 57%). In contrast, women presenting with angina had more favourable risk profiles than did women with other coronary disease presentations, for example myocardial infarction. They tended to be younger, have lower plasma cholesterol levels and a lower incidence of diabetes mellitus, hypertension and smoking.

Subsequent myocardial infarction rates differed in women but not in men according to their initial coronary disease presentation. After 10 years of follow-up, myocardial infarction was twice as likely to occur in...
women whose initial presentation was myocardial infarction rather than angina (34.8% vs 17.8%). Similar to men, the coronary death rate during follow-up was highest in women first presenting with myocardial infarction and lowest in those women first presenting with angina. Women presenting with myocardial infarction fared at least as badly as men, which could not be accounted for by their older age at presentation.

**Chest pain and normal coronary arteries**

The Framingham[5-7] and other[8] studies highlight several differences between men and women with angina, in particular the better outlook of women. In contrast, when the diagnosis is very likely to be correct, such as in recognised myocardial infarction, women fare less well than men. One possible explanation for the better prognosis of women with angina is that the chest pain may not have been cardiac in origin in all cases. Because cardiac catheterization was not used to establish a diagnosis of angina, it is likely that a significant proportion of the women did not have coronary artery disease. Many studies have shown a higher incidence of normal coronary arteries in women catheterized because of chest pain compared with men[9]. For example in the Coronary Artery Surgery Study (CASS) 50% of women undergoing coronary angiography for chest pain had either minimal or no coronary artery narrowings[10].

The large number of women with chest pain and normal coronary arteries in studies such as the CASS registry beg the question of whether the pain could still be cardiac in origin despite angiographically normal coronary arteries. Ever since the term syndrome X was introduced by Kemp in 1973 to describe patients with chest pain, an abnormal exercise test response and angiographically normal coronary arteries[11] there have been numerous published studies investigating the phenomenon. The observed impairment of coronary flow reserve in some patients despite apparently normal epicardial coronary arteries[11,12] raises the possibility of an abnormality at the level of the coronary microvasculature, so-called microvascular angina[13]. However, the underlying pathogenetic mechanism(s) is not well understood[14] and proof of myocardial ischaemia in these patients is difficult[15].

Although an epicardial coronary artery may appear normal angiographically it is possible that early pathological changes exist, not detectable using standard angiographic techniques, that could have functional effects on coronary blood flow. A recent study by Wiedermann et al[16] demonstrated distinct abnormalities of coronary artery morphology assessed by intravascular ultrasound in over 50% of patients with syndrome X. Patients with these morphological abnormalities also had an abnormal response to exercise, with epicardial vasoconstriction rather than vasodilatation. It is, therefore, not surprising that so many different and sometimes conflicting observations have been made in patients with syndrome X, since we now recognise the limitations of the term ‘angiographically normal epicardial coronary arteries’.

From a clinical perspective it is often impossible to determine whether or not chest pain is cardiac in origin in the presence of angiographically normal coronary arteries and it is impractical, in routine clinical practice, to resort to sophisticated techniques for detecting myocardial ischaemia, for example studies of myocardial lactate production and changes in coronary sinus potassium and hydrogen ion concentration. More important is the recognition that the prognosis of patients with chest pain and ‘normal’ coronary arteries is good and cardiac events are rare[17,18] and the patients should be appropriately reassured.

**Cardiovascular risk factors in women**

The vast majority of studies investigating cardiovascular risk factors and the effects of risk factor modification have been predominantly, or exclusively, conducted in men. Less information is available with regard to cardiovascular risk factors for women. Although the major risk factors are similar in men and women there are certain gender differences, described below.

**Cigarette smoking**

As a risk factor for coronary artery disease, cigarette smoking has become increasingly important in women. A recent editorial described smoking in women as the tragedy of the majority[19], since the decline in smoking during recent years has been considerably greater among adult men than women. Tobacco advertising has specifically targeted women such that more young women than young men smoke today. The introduction of low-tar brands has done little to reduce the risk of heart disease among women[20].

Cigarette smoking is a major risk factor for coronary artery disease in women, in particular myocardial infarction, although the association is less strong for angina[21-23]. A clear dose-response relationship between the number of cigarettes smoked per day and the risk of fatal and non-fatal heart disease was demonstrated in the Nurses Health Study[22]. Among heavy smokers (≥25 cigarettes per day) the relative risk was 5.5 for fatal coronary heart disease, 5.8 for non-fatal myocardial infarction and 2.6 for angina pectoris. Furthermore, there was no safe level of smoking for women — light smokers of 1 to 4 cigarettes per day had more than a twofold increase in risk of fatal coronary heart disease. The greatest risk was among women smokers already at increased risk because of other factors such as older age, hypertension, diabetes mellitus or hypercholesterolaemia, in contrast to former smokers in whom there was little, if any, increase in risk.
Diabetes mellitus

Whereas most coronary risk factors are better tolerated by women than men, diabetes mellitus remains an exception to the rule. Diabetes mellitus is more prevalent amongst women with coronary artery disease than amongst men, and it appears to be a stronger risk factor for women, such that the risk of coronary artery disease in diabetic women approaches that in diabetic men. In the Framingham study, diabetes mellitus was a greater risk factor for myocardial infarction in women than in men, and even exceeded the risk imposed by cigarette smoking. Diabetes mellitus was associated with obesity, hypertension and hypercholesterolaemia but, even after adjustment for other risk factors, the relative risk for coronary artery disease amongst diabetics was more than doubled compared with non-diabetics. In the Nurses Health Study diabetes was associated with a more than six-fold increased risk of non-fatal myocardial infarction and fatal coronary heart disease during 8 years of follow-up.

Hypertension

Blood pressure rises more steeply in women such that, after the age of 50 years, hypertension is more prevalent among women than among men. Hypertension, including isolated systolic hypertension, is an independent risk factor for coronary artery disease in both men and women at all ages and is a more important risk factor in women. A history of hypertension is frequently found in men and women with coronary artery disease and is more common in women. Many studies have shown that hypertension in women is an important risk factor for myocardial infarction and, to a lesser extent, angina.

Although the benefits of treating severe hypertension are well recognised there is little evidence that lowering blood pressure in mild-to-moderately hypertensive women is beneficial. Several large trials have not included women, for example the Veterans Administration trials, the Oslo study and the Multiple Risk Factor Intervention Trial (MRFIT) (for review see). One of the most comprehensive studies of the treatment of hypertensive women was the Hypertension Detection and Follow-up Program Cooperative Group study, which examined the effects of antihypertensive therapy on 5 year morbidity and mortality. Treatment was associated with a 27-8% reduction in mortality in black women and a small (2-3%) increase in mortality in white women. Similarly, the Medical Research Council (MRC) trial, in which 48% were women and most were white, demonstrated a 26% increase in all-cause mortality in women. In contrast, drug treatment of older women with isolated systolic hypertension, which is more common in women than men, has been shown to be effective in reducing both stroke rates and coronary artery disease.

In summary, the consequences of treating hypertensive women depend on race, the severity of hypertension and whether or not there is isolated systolic hypertension. Lowering mild-to-moderately elevated blood pressure in white women may be harmful.

Plasma lipoproteins

The relationship between serum lipids and coronary heart disease has been examined in prospective studies. Most studies, but by no means all, have demonstrated an association between elevated total cholesterol levels and risk of coronary artery disease in women, although women appear to be at less risk compared with their male counterparts for a given cholesterol level. HDL-cholesterol, which tends to be higher in women at every age, is a powerful predictor of coronary disease risk in women but, because levels are higher in women, the total cholesterol/HDL-cholesterol ratio is a better predictor of coronary disease risk in women than the unadjusted total cholesterol. In the Lipid Research Clinics Follow-up Study, HDL cholesterol was second only to age as a predictor of cardiovascular death among women. Elevated plasma triglycerides may be a marker of coronary disease risk in women but not in men, at least in univariate analyses. This association may, however, be lost after adjustment for other serum lipids, suggesting a limited role for screening serum triglycerides levels in women.

Hormonal factors

The incidence of coronary artery disease rises after the menopause, whether natural or surgically induced. Consequently, the oestrogen status of a woman has been considered an important factor with regard to coronary artery disease risk. Hormonal status, use of the contraceptive pill (and type of preparation) and the use of oestrogen replacement therapy have been extensively studied with regard to the development of coronary artery disease. Whether other hormonal and biochemical changes which occur at the menopause are also important is unknown.

Epidemiological studies have shown a relationship between oestrogen lack and increased risk of coronary artery disease. Oestrogen replacement in postmenopausal women appears to be beneficial in this respect. Observational studies indicated that oestrogen use in healthy postmenopausal women is associated with a risk reduction of approximately 50% for coronary heart disease, an effect which may persist for several years after discontinuation of therapy. Furthermore, angiographic studies have demonstrated a lower degree of coronary artery occlusion in users of postmenopausal oestrogen compared with non-users. However, most of these studies were conducted in the United States using conjugated equine oestrogen preparations taken orally without added progestins. The precise role of currently prescribed regimes of hormone replacement, and the effect of added progestin,
on primary and secondary prevention of coronary heart disease, is unknown. Furthermore, the magnitude of the benefit reported in early trials may, in part, be explained by unintended selection of relatively healthy women for oestrogen replacement[47]. Large clinical trials evaluating the role of hormone therapy on primary (Women's Health Initiative) and secondary (Hormone Estrogen/Progestin Replacement Study) prevention of coronary artery disease are currently in progress in the United States but results are not expected for some years.

The protective effect of oestrogen is probably due to many factors. Oral oestrogen therapy lowers plasma LDL-cholesterol and raises plasma HDL-cholesterol, which may account for part of the beneficial effect of oestrogen replacement[48]. However, the Lipid Research Clinics Program Follow-up Study[49] demonstrated that less than half of the beneficial effect on mortality due to coronary heart disease could be explained by changes in plasma lipid concentrations. Other possible actions of oestrogen replacement include improved glucose and insulin levels[49] and the modulation of vasomotion[50].

The question of whether the addition of a progestin in combination hormone replacement therapy alters the beneficial effects of oestrogens was addressed in the recently published Postmenopausal Estrogen/Progestin Interventions Trial[51]. Oral oestrogen taken alone or in combination with a progestin was associated with improved lipoprotein levels compared with placebo. HDL levels rose with treatment although the rise was smaller in the combined treatment groups compared with the oestrogen alone group. However, women taking unopposed oestrogens had a significantly higher rate of adenomatous or atypical endometrial hyperplasia, making combination therapy mandatory in women with a uterus.

Other factors

Obesity is associated with hypertension, diabetes mellitus and hypercholesterolaemia in women but is probably not an independent risk factor per se for coronary artery disease[25]. However, the pattern of abdominal fat distribution may be important. Compared with a gynoid fat distribution, the android fat distribution with central fat deposition is related to excess cardiovascular complications in both men[52] and women[59,53].

Moderate alcohol consumption appears to have a cardioprotective effect in men and women. In a study of 1048 British women, moderate alcohol consumption (1–20 g . day$^{-1}$) was associated with lower cholesterol and triglycereide concentrations and lower insulin levels, suggesting that the beneficial effect might be due to an increase in insulin sensitivity[54]. The findings of a larger prospective study on the effects of alcohol consumption and mortality among 85 709 women have been recently published[55]. Light-to-moderate drinking (1.5–29.9 g. day$^{-1}$) was associated with a decrease risk of cardiovascular death but this benefit was largely confined to women at greater risk of coronary artery disease.

Non-invasive assessment of women with chest pain

Clinical history

The first presentation of coronary artery disease is most likely to be with angina in a women and myocardial infarction in a man[56,57]. A diagnosis of myocardial infarction is generally easily made, but a diagnosis of angina is more difficult, especially in women. The nature of the chest pain is less predictiv of the presence of angiographic coronary artery disease in women[56,57]. In one series, coronary artery disease was present in 35–65% of women with typical angina compared with less than 20% of women with atypical symptoms[58]. These studies highlight the value of the clinical history in establishing a diagnosis in women. The more typical the chest pain is of angina, the more likely it is that a women has underlying coronary artery disease. However, even when the history is highly suggestive of cardiac chest pain, a significant proportion of women are subsequently found to have angiographically normal coronary arteries. The reasons for these sex differences are uncertain, but other causes of chest pain, for example syndrome X, mitral valve prolapse and coronary artery spasm are more frequently found in women.

Therefore, to be confident that the symptom of chest pain is indicative of underlying coronary artery disease, women may require more extensive investigation compared with their male counterparts. However, studies have indicated that women are less likely than men to undergo investigation[55,56,57], which suggests that some women are incorrectly diagnosed as having coronary artery disease when they do not, and vice versa. The social and economic ramifications of misdiagnosis should encourage physicians to investigate thoroughly all women who present with chest pain for further evaluation.

The extent to which a physician investigates the patient with chest pain depends on many factors, such as the severity of the symptoms, the perceived likelihood of coronary artery disease and the response to standard anti-anginal therapy. Ease of access to facilities for further investigation and social and cultural factors may also influence patient management. Coronary arteriography is the gold standard by which all other investigative techniques are measured but it is not always readily available and, furthermore, it carries a small but well-defined risk to the patient. Currently, no single non-invasive test is of value for large-scale screening in asymptomatic women. Because the prevalence of coronary artery disease is lower in women compared with men, the value of any investigation will be lower. Consequently, the results of any one test should be interpreted with this in mind.
Exercise testing

Exercise testing is a readily available, low-cost and non-invasive method for the assessment of chest pain syndromes. However, the electrocardiographic response to exercise is influenced by the prevalence of the disease in the population studied. Detry et al.\(^6\) showed that the diagnostic value of the exercise test result differed between the sexes and within a given sex, and that these differences were related to the prevalence of coronary artery disease. For example, the false-positive rate was higher when coronary artery disease was uncommon and the false-negative rate was higher when coronary artery disease was common. For these reasons, ECG changes with stress in the absence of coronary artery disease are far more frequently observed in women\(^{38,61}\).

Correction for the prevalence of coronary disease, that is the pre-test likelihood, and other factors contributing to false-positive exercise tests in women results in comparable diagnostic accuracy of exercise tests in men and women\(^{62,63}\).

The positive predictive value of exercise testing in women can also be improved if the nature of the chest pain is considered. Weiner et al.\(^{62}\) demonstrated that the majority of false-positive exercise tests occurred in women with atypical chest pain. Similarly, Guiteras et al.\(^{64}\) found the predictive value of a positive exercise test was 83% in women with atypical angina, falling to 50% in women with probable angina — in other words, no better than tossing a coin. The diagnostic accuracy of exercise testing can be improved in other ways. The specificity of exercise testing increases if greater degrees of ST segment depression are required for a 'positive' test, for example 0.2 mV rather than the more usual 0.1 mV. Profound ST segment depression is more likely to represent a true-positive result compared with lesser degrees of depression\(^{61}\), as is widespread ST segment depression, especially if recovery is prolonged\(^{64}\). However, if a risk profile for coronary artery disease, created from information provided in the patient's clinical history, is taken into account, the additional value of exercise testing for establishing the diagnosis is small. For instance, Goldman et al.\(^{65}\) showed that when certain clinical variables, for example age, cholesterol concentration, history of myocardial infarction, sex, typical angina and smoking history were considered, the additional value of exercise testing was minimal.

These findings do not imply that exercise testing should be abandoned in women, but that the result should be interpreted in the clinical context, and not in isolation. There is little diagnostic value in performing an exercise test in women with atypical symptoms. Similarly, no value should be attached to a negative result in the presence of an inadequate workload, since this may well represent a false-negative result. Patients unable to exercise adequately due to age or concomitant disease can be investigated in other ways, for example by pharmacological stress imaging with scintigraphy or echocardiography. In the presence of an adequate exercise tolerance a negative result has a high predictive accuracy\(^{62}\). Women with a positive exercise test result should be investigated further to establish the diagnosis.

Thallium scintigraphy

Thallium scintigraphy combined with exercise and/or pharmacological stress is a reliable method for the detection of reversible myocardial ischaemia. Unfortunately, important sex differences exist which limit the use of thallium imaging in women. Breast tissue attenuates the radiation signal and may produce an apparent perfusion defect, typically located in the anteroseptal region. Careful positioning and the advent of new techniques, for example SPECT imaging, may lessen the problem although this has yet to be demonstrated.

The value of thallium scintigraphy, like exercise stress testing, is influenced by the prevalence of coronary artery disease in the population. Combining the results of thallium imaging and exercise testing increases the predictive value. When the prevalence of coronary artery disease is low, an abnormal exercise test response or thallium scintigraphy has low predictive value, but concordant abnormalities are significantly more predictive\(^{66}\). Thallium scintigraphy may be particularly useful in women with probable angina, rather than typical angina, based on history alone, since the likelihood of a false-positive exercise test is so high in this group.

Stress echocardiography

Interest has grown in recent years in the use of stress echocardiography for the assessment of patients with suspected coronary artery disease. Studies of exercise stress and pharmacological stress echocardiography in women have been encouraging, suggesting that stress echocardiography may be more predictive than standard exercise electrocardiography. In a study of 83 consecutive women evaluated for chest pain, dipyridamole echocardiography was of greater diagnostic value than exercise testing\(^{67}\). Whereas the sensitivity was similar (79% vs 72% respectively), dipyridamole-echocardiography had greater specificity (93% vs 52%) and positive predictive value (91% vs 57%).

Other techniques

Cardiac fluoroscopy is rarely used for diagnosing coronary artery disease, and yet the presence of coronary artery calcification detected by fluoroscopy may be as sensitive as a positive exercise test in women with suspected coronary artery disease\(^{63}\). Radionuclide ventriculography, which has also been evaluated for the detection of coronary artery disease, is rarely used as a clinical tool for investigating patients with chest pain since there are striking gender differences in the ejection fraction response to exercise\(^{68}\).
Coronary arteriography

Coronary arteriography remains the gold standard for establishing a diagnosis of coronary artery disease. However, studies suggest that women are less likely to be referred for cardiac catheterization\(^1,59,60\). Several reasons may account for this apparent sex bias. Coronary artery disease may be perceived as being more severe in men because of their higher incidence of the disease. Revascularization procedures are generally viewed as being less effective in women\(^69,70\), which may influence the extent to which the physician investigates chest pain in women. Additionally, the lower sensitivity and specificity of many of the preliminary non-invasive tests frequently used in the early stages of diagnosis may affect referral patterns.

The CASS study demonstrated that the age and sex of the patient, and the character of chest pain, were all important determinants of disease prevalence and severity. In this study, the prevalence of significant coronary artery stenoses and left main stenoses were evaluated in 20,391 patients who underwent coronary arteriography because of chest pain\(^59\). The disease prevalence was related to the nature of the chest pain, and was lower for women in all categories of chest pain. The percentage of men and women with significant coronary artery disease who had definite angina was 93% vs 72%, compared with 66% vs 36% for probable angina and 14% vs 6% for nonspecific chest pain.

Of course, the demonstration of epicardial coronary artery disease need not imply that the patient's chest pain is due to reversible myocardial ischemia. If the symptoms are atypical and refractory to standard anti-anginal drugs then it is quite possible that another cause exists. Conversely, the absence of demonstrable coronary artery disease does not exclude a diagnosis of chest pain of cardiac origin in all cases. In a minority of patients microvascular angina, or syndrome X, and coronary artery spasm may give rise to angina despite angiographically normal coronary arteries. These conditions are uncommon but occur more frequently in women than in men.

Conclusions

The importance of coronary artery disease as a major cause of morbidity and mortality amongst women is now well established. Studies suggesting that women with suspected heart disease are managed differently to men should encourage us to understand such discrepancies and, where appropriate, to alter our practice. If we judge our diagnostic acumen by the predictive value of exercise testing then we are not only failing to detect a considerable proportion of women with established coronary artery disease but we are also investigating many women who will subsequently be shown to have angiographically normal coronary arteries. The lesser value of non-invasive tests in women makes it difficult to reduce the number of patients subsequently found to have normal angiograms but recognition of the diagnostic difficulties facing us is the first step towards improving the management of women with chest pain.

Careful history taking and the creation of a risk factor profile are of value in determining how far one should investigate a women with chest pain. A women with atypical chest pain and few or no risk factors for coronary artery disease should be reassured and the opportunity should be taken to educate her about primary prevention to minimise her risk of developing heart disease in the future. At the other end of the spectrum, women with typical symptoms and risk factors for heart disease should be investigated further. Because all non-invasive tests are of less value in diagnosing coronary artery disease in women, the threshold for coronary arteriography should be lower, since the consequences of a diagnosis of coronary artery disease are considerable and lifelong. The precise cause of chest pain in patients with angiographically normal coronary arteries is frequently elusive, but at least the patient can be reassured that her prognosis is good.

References

**Review**


