Published in final edited form as:
J Nucl Cardiol. 2011 February ; 18(1): 144–152. doi:10.1007/s12350-010-9315-2.

Sex Differences in the Diagnostic Evaluation of Coronary Artery Disease

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Although sex differences in coronary heart disease (CHD) have long been recognized, many of the recommendations for the management of female patients continue to be identical to male patients. Given the paucity of sex-specific data in basic science and clinical studies, however, defining unique diagnostic and therapeutic strategies for women remains problematic for scientists and clinicians. For instance, women represent only 38% of subjects in previously NIH-funded cardiovascular studies (1). Previous studies and clinical trials have also included inadequate numbers of women. Finally, only 25% of previous cardiovascular clinical trials have reported sex-specific results (2).

Recently, researchers have been encouraged to report sex differences in basic and clinical studies. Much of the impetus originates from data indicating that more women die of cardiovascular disease (CVD) than men (3). This disparity in mortality may signal the need for sex-specific guidelines for the diagnosis of CHD. In this review, we will discuss sex differences in the clinical manifestations and outcome of CHD, the limitations of current approaches for the management of female patients, and the potential strategies to improve the evaluation of CHD in women.

SEX DIFFERENCES IN THE CLINICAL MANIFESTATIONS AND OUTCOMES OF CORONARY ARTERY DISEASE

CHD may have different clinical manifestations in younger women (<65 years) compared to older women and men. For example, younger women are more likely to report typical angina than older women and men. In a recent meta-analysis of 74 international studies, which included 13,331 women and 11,511 men, the prevalence of typical angina was 11–27% greater for women <65 years than women ≥75 years of age and men (4). Compared to men, younger women were also more likely to present atypically (e.g., rest pain, prolonged chest pain not relieved with rest, diaphoresis, jaw pain, and fatigue in absence of chest pain) (5).

Although younger women are more likely to have angina, they are less likely to have obstructive disease on coronary angiography. In a detailed analysis of women with suspected ischemic CHD enrolled in the Women's Ischemic Syndrome Evaluation (WISE), >50% had non-obstructive coronary artery disease (<50% stenosis), while the remaining had

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minimal to no detectable disease (6). Non-obstructive coronary artery disease (CAD) is also more frequently found in younger women presenting with acute coronary syndrome (ACS). In a recent analysis of national registry data in >450,000 women (average age of 64±13 years), those presenting with ACS had a 50% lower likelihood of having obstructive disease than age-matched men (7). Similarly, women presenting with ST elevation myocardial infarction have higher rates of non-obstructive disease than men, 10–25% compared to 6–10% (8).

Historically, the prognosis for non-obstructive disease was considered benign (9–11). Recent data form the WISE study, however, suggest that women with non-obstructive disease and atypical chest pain have a two-fold greater risk of non-fatal myocardial infarction than asymptomatic women (12). Those who have more typical angina and ischemia have an even higher mortality (13). A recent study reported that the 5-year CVD event rates were 16%, 7.9%, and 2.4% in women with <50% stenosis, women without stenosis, and those without symptoms, respectively (14). In addition, >50% of symptomatic women without obstructive disease continue to have signs and symptoms of ischemia and undergo repeat diagnostic procedures and hospitalizations (15, 16). Comparative prognostic data in men with non-obstructive CHD are currently not available.

LIMITATIONS OF CURRENT APPROACHES FOR THE MANAGEMENT OF WOMEN

It remains unclear why women continue to have higher overall mortality than men despite less obstructive disease (Figure 1) (3). The reduction in mortality from CHD for women has also lagged behind that for men, and has even increased in younger women over the last several years (17). One proposed explanation attributes the higher mortality to advanced age and a higher rate of co-morbidities, because CHD presents 10 years later in women than men (18). However, this does not explain why most of the mortality difference is observed in younger women (17). For example, in a study of >300,000 patients from the National Registry of Myocardial Infarction-2, the adjusted mortality rate was twice as high among women <50 years of age than men (19). In the Thrombolysis In Myocardial Infarction-II trial, women had significantly greater rates of death and re-infarction at 6 weeks and 1 year, even after adjustment for age and co-morbidities (20, 21).

Another possible explanation is that women may receive fewer diagnostic tests, experience more treatment delays, and are given less aggressive therapy than men. Previous studies have shown that women with suspected obstructive CHD underwent fewer stress tests and diagnostic angiograms than men (22–25). Women often experience treatment delays and receive less aggressive therapy (26, 27). A previous registry study showed that women were less likely to have an electrocardiogram performed within 10 minutes of presentation (25.2% for women vs. 29.3% for men) and were less commonly cared for by a cardiologist during their inpatient hospitalization (53.4% for women vs. 63.4% for men) (26). Women also received less acute medical treatment after myocardial infarction than men, including less heparin (80% vs. 84%) and glycoprotein IIb/IIIa inhibitors (28.7% vs. 38.6%) (26). At discharge, women did not receive aspirin (87.5% vs. 90.4%), beta blockers (80.5% vs. 82.7%), and statins (55.9% vs. 69.4%) as frequently as men (26). Most of these findings are based on data in early 2000. As more and more women and physicians become aware that CVD remains the leading killer in women, the underutilization of diagnostic and treatment strategies should dissipate, which may account for similar decreases in mortality in women and men since 2000 (Figure 1) (3).

A final explanation for the higher overall mortality in women is that the current diagnostic paradigm may be suitable for men, but may not be appropriate for all women (18, 28). For

example, non-traditional risk factors which are more common in women, such as decreased heart rate variability and lower levels of physical activity, are not accounted for by current risk stratification algorithms (29). There may also be unique factors to women, such as cyclic hormones and pregnancy associated vasculature changes, which may alter the pathophysiology of CHD (Figure 2). This may explain why plaque erosion rather than plaque rupture more likely precipitates ACS in women, why women have more positive remodeling and less anatomical obstruction, and why women have more coronary dysfunction (i.e., endothelial dysfunction and microvascular disease) than men (30–32). Finally, anatomically, women have smaller vessels than men, even after correction for body surface area, so even mild disease may be more harmful in women than men (19, 33). Thus, it is possible that setting an intervention threshold of 70% for significant disease, which is based on earlier studies in men, may be too high for women.

POTENTIAL STRATEGIES TO IMPROVE THE EVALUATION OF CHD IN WOMEN

Although further studies are needed, cardiovascular medicine experts have recently proposed changing the paradigm for the diagnostic evaluation of CHD in women (18, 34). These modifications include amending risk stratification models in women, changing current recommendations for diagnostic testing to improve sensitivity and specificity in women, and adding coronary function testing to evaluate non-obstructive disease (<50% stenosis) in women (Figure 3).

Risk Stratification for Asymptomatic Women

One proposed modification is the addition of nontraditional risk factors, biomarkers, and noninvasive imaging to improve risk stratification in asymptomatic women. Traditional risk factor counting and the Framingham risk score may underestimate risk in women. In a previous survey of >13,000 participants, the Framingham Risk Score classified >90% of women <69 years of age as low risk (17). Specifically, the study showed that 2%, 8.5%, and 44.1% of women compared to 59.4%, 90.8%, and 97.5% of men aged 50–59, 60–69, and 70–79 years, respectively, were classified as intermediate risk.

Current risk stratification models may underestimate risk in women because there are significant sex differences in the prevalence of traditional and nontraditional risk factors and the effect of these risk factors on outcome. For example, cardiovascular mortality in diabetic women is almost three times higher than in diabetic men (34, 35). In addition, high triglyceride and low levels of high-density lipoprotein cholesterol are more prominent and more potent independent risk factors for CHD in women than men (36). Women with metabolic disturbances, including abdominal obesity, features of the metabolic syndrome, low estrogen, and low testosterone, may also be at a higher risk (28). In addition, women have greater mean C reactive protein (CRP), an inflammatory marker, which increases proportionally with the risk of future cardiac events and has been associated with accelerated CHD risk in women when combined with traditional risk factors (18, 37). Based on these findings, a sex specific risk score (i.e., the Reynolds Risk Score) was derived (n=24, 588) and later validated (n=8,158) in large cohorts of women (38). The score incorporates high sensitivity CRP, systolic blood pressure, high density lipoprotein cholesterol, total cholesterol, hemoglobin A1C, and smoking. When compared with the Framingham Risk Score, the Reynolds score resulted in the correct reclassification of >40% of women at intermediate risk (38).

Another approach to improve risk stratification is to use noninvasive imaging to detect subclinical disease, which includes the application of the ankle-brachial index, carotid

intimal thickness, coronary artery calcium score (CAC), and brachial flow mediated dilation (Figure 3) (18). For women, an abnormal ankle brachial index of ≤0.90 increases with age and has a prevalence ranging between <5% for women <60 years to 10%–35% for those 60–80 years old (18). For an ankle brachial index ≤0.90, the hazard ratio for death is 2.7 (95% CI: 2.0 to 3.6) for women and 3.3 (95% CI: 2.7 to 4.1) for men (39). For carotid intimal thickness (cIMT), another validated measure of subclinical disease, a negative cIMT is associated with a ~1% and ~3% risk in women and ~11% and ~14% risk in men, respectively (40). Coronary artery calcium is another imaging measure that detects subclinical disease. Similar to obstructive CAD, its incidence in women lags behind men. Based on a NHLBI Multi-Ethnic Study of Atherosclerosis, women with a CAC score ≥300 had an annual CHD event rate of 2.2%, placing them at a high risk for CHD, thus warranting more aggressive treatment (41). Of note, women with a high CAC score and multiple risk factors have a 10% greater CHD event risk than men with a similar risk profile (42). Finally, flow-mediated dilation, a noninvasive test for endothelial dysfunction (which is the earliest manifestation of CHD), may emerge as another promising measure to improve risk stratification in asymptomatic women, although currently it has mainly research applications.

Diagnosis and Risk Stratification in Symptomatic Women

In addition to improving the risk stratification of asymptomatic patients, amending the correct paradigm for the diagnosis and risk stratification of symptomatic women may be warranted (Figure 3). Similar to men, only symptomatic women with intermediate to high pre-test probability of CHD should undergo noninvasive testing. Unlike symptomatic men, symptomatic women may have more non-obstructive disease in addition to single vessel disease than age-matched men, which can decrease the diagnostic accuracy and result in a higher false positive rate (34).

Treadmill testing is the most common noninvasive evaluation for suspected ischemia, but its continued application in women remains contentious. In a meta-analysis evaluating ECG testing for women, sensitivity and specificity were 61% and 70%, respectively (43). In comparison, a meta-analysis in men showed a slightly higher sensitivity and specificity of 72% and 77%, respectively (44). One previous study directly compared the sensitivity and specificity of treadmill testing in 3,213 women vs. 5,458 men using myocardial perfusion as the reference standard. Although more women (14%) than men (10%) had a false positive ECG ($p<0.001$), the false-negative rate was considerably lower in women (17% vs. 32%, $p<0.001$) (45). Compared with men, women had lower test sensitivity (30% vs. 42%, $p<0.001$) and positive predictive value (34% vs. 70%, $p<0.001$) but higher specificity (82% vs. 78%, $p = 0.002$), negative predictive value (78% vs. 52%, $p<0.001$), and accuracy (69% vs. 58%, $p<0.001$). In the smaller subset of patients referred for coronary angiography (205 women, 838 men), the false-positive electrocardiographic rate was again higher in women (13% vs. 7%, $p = 0.003$), but neither specificity (69% vs. 74%, p = NS) nor accuracy (60% vs. 66%, p = NS) was different between the sexes.

The accuracy of treadmill testing in women can be improved by adding multiple parameters, such as chronotropic and hemodynamic response and maximal exercise capacity, to ST segment evaluation (34). For example, integrative tests scores, such as the Duke Treadmill score, have been shown to improve accuracy and provide sex-specific data (34). In a study of 976 symptomatic women who underwent treadmill testing and were then referred to angiography, significant stenosis was present in 19%, 35%, and 89% of low-, moderate-, and high-risk women, respectively, based on the Duke treadmill risk categories (46). The 5-year CHD death rates ranged from 5% to ≥10% for women vs. 9% to ≥25% for men with low to high risk Duke treadmill scores. Based on these data, women with a high Duke treadmill score have a high probability of obstructive disease and should be referred for

invasive testing (34). Those with an intermediate Duke treadmill score should be referred for stress testing with imaging. Other important parameters include the maximal exercise capacity and heart rate recovery measurement (1–2 minutes after exercise), which provide near- and long-term outcome in large cohorts of women (47, 48). Women who exercise <5 metabolic equivalents (METs) are at an increased risk for death and should be referred for pharmacologic stress testing (49). Those who have ischemia at low workloads (<5 METs) also have a high likelihood of obstructive disease and should be referred for invasive angiography (34). Thus, current guidelines encourage the use of comprehensive data from treadmill testing to risk stratify women with suspected ischemia (34).

For women with suspected CAD and an abnormal resting, both stress echocardiography and myocardial perfusion provide valuable diagnostic and prognostic data. Based on aggregate data, stress echocardiography provides improved sensitivity and specificity and diagnostic accuracy with no differences between the sexes; however, most studies have not been corrected for post-test referral bias and post-test verification bias (34). Similarly, prognostic information by stress echocardiography is comparable in women and men. The presence of an abnormal stress echocardiography is associated with a high risk of future adverse cardiac events; conversely, a normal study confers a low risk (50–53). Stress echocardiography has been shown to provide incremental prognostic data beyond that provided by clinical and exercise variables (27, 34, 54). Based on a multi-center registry data, exercise stress echocardiography may also be more cost effective than treadmill exercise testing, given that the higher rate of false positives using treadmill exercise testing likely leads to more unnecessary angiography tests and expense (55). Nevertheless, there is insufficient data to recommend exercise stress echocardiography as the initial test in all women, and it should still be reserved for women with suspected CAD and an abnormal resting ECG (34).

The assessment of myocardial perfusion by gated single positron emission tomography (SPECT) is another noninvasive technique for the diagnosis and risk stratification of women with suspected obstructive CAD. Historically, myocardial perfusion imaging has been reported to have a high number of false positives in women, possibly due to breast attenuation and a smaller average heart size (56). Specificity has improved with advancement in nuclear imaging technology and is now only slightly lower than stress echocardiography (Table 1). Similar to stress echocardiography, myocardial perfusion provides incremental prognostic information to clinical and exercise variables for both women and men (34). In a recent multi-center registry of 5009 men and 3402 women, the number of territories with perfusion defects was associated with cardiac mortality in women and men (57). In women, the number of abnormal territories remained the strongest correlate of mortality after adjustment for exercise variables. In the setting of a normal perfusion study, the annual cardiac event rate is <1% compared to a significantly increased risk of cardiac death in the setting of an abnormal perfusion study (58).

Overall, noninvasive testing appears to be a more valuable for risk stratification than diagnosis of obstructive CAD. The sensitivity and specificity can be as low as ~55% and even lower if diagnostic accuracy is corrected for referral bias. The “false” positives in noninvasive testing, however, may in part reflect the presence of coronary dysfunction, which is associated with increased morbidity and mortality, rather than the limitation of noninvasive testing

Measuring coronary function has emerged as an important step in the evaluation of patients with suspected ischemia. In a recent study, the incorporation of fractional flow reserve, a measure of the functional significance of an anatomical lesion, to guide percutaneous coronary intervention has been shown to reduce the number of stents used as well as to improve morbidity and mortality (59). Detecting endothelial dysfunction and microvascular

disease as a cause of chest pain and ischemia even in the absence of significant stenosis may also provide important diagnostic and prognostic information as well as reassurance to patients. In the cardiac catheterization lab, the measurement of endothelial function and microvascular function is achieved by measuring the change in coronary diameter in response to acetylcholine challenge and by measuring the index of microvascular resistance using a coronary pressure wire. In patients undergoing diagnostic angiography, single vessel percutaneous coronary intervention, or post myocardial event, the presence of coronary dysfunction was associated with major adverse cardiac events (60, 61). Although treatment regimens have not clearly been identified, improvement of coronary function has been shown to decrease the rate of major adverse cardiac events when compared with no improvement (62). Although invasive coronary angiography remains the gold standard for the evaluation of coronary function for the time being, the development of a noninvasive measure is needed to risk stratify asymptomatic patients, diagnose coronary dysfunction in those presenting with chest pain, and monitor therapy (27, 54).

CONCLUSION

CHD remains the leading cause of death in both men and women. Sex differences in the clinical presentation and manifestation of CAD may warrant the development of guidelines specific for women as opposed to men. Future investigation should evaluate diagnostic and treatment strategies to optimize outcome in women and men.

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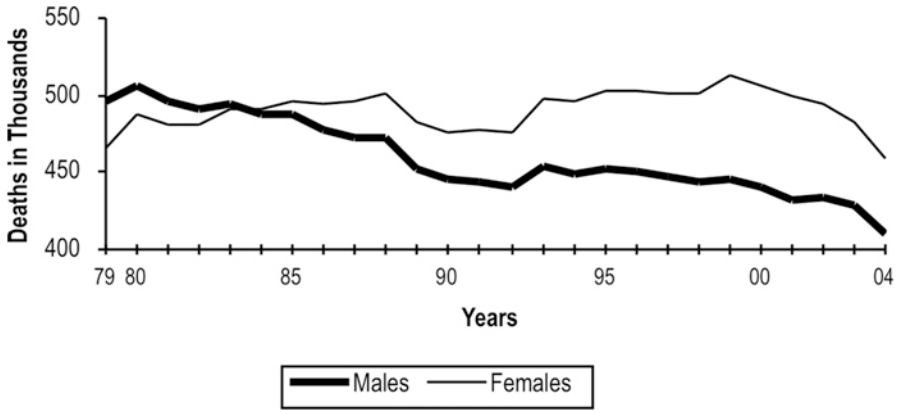

Figure 1.

Death from cardiovascular disease in the United States from 1979 to 2005 in women and men (3). Overall mortality from cardiovascular remains higher in women than men. Reduction in mortality has previously lagged behind men but has shown similar declines since 2000.

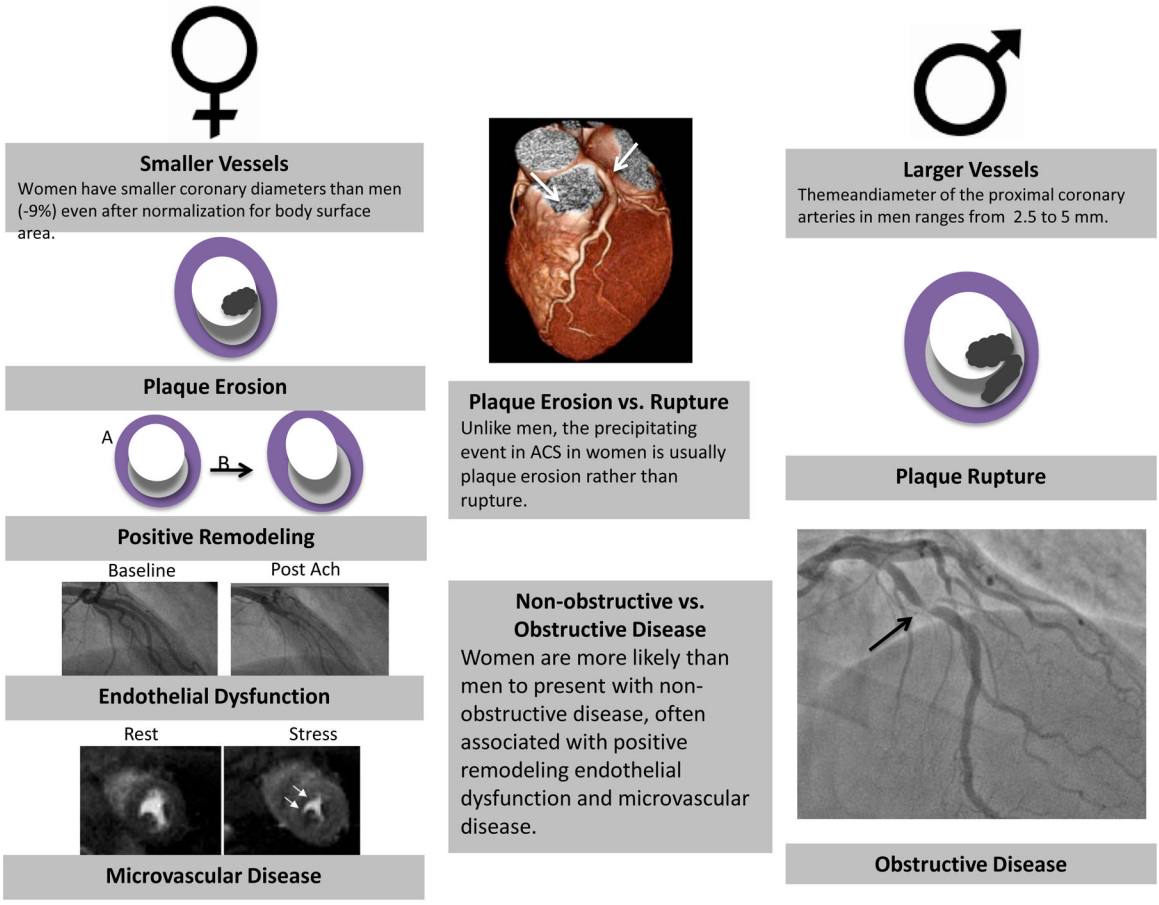

Figure 2.

Coronary heart disease may have different clinical manifestations. Women may have different clinical manifestations of coronary heart disease than men. Because women have smaller arteries, they may be more susceptible to even the slightest mismatch in demand and supply. Women may also be more prone to plaque erosion and the development of coronary dysfunction than men.

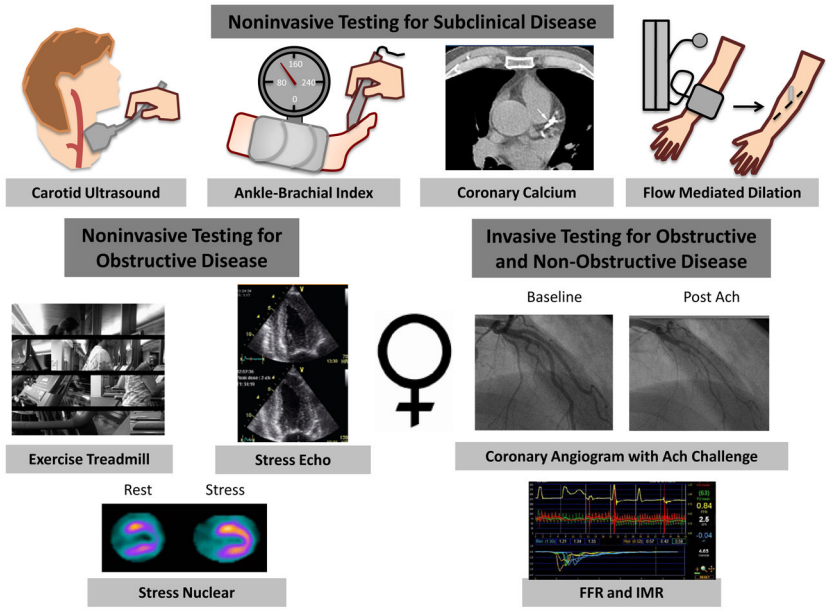

Figure 3.

A new paradigm for the diagnosis and risk stratification of women with suspected CHD. Asympatomatic women may benefit from further risk stratification with noninvasive tests designed to detect subclinical disease. Symptomatic women may benefit from the addition of coronary function testing including measuring fractional flow reserve, response to acetycholine, and the index of microvascular resistance to guide therapy. Ach: acetycholine, FFR: fractional flow reserve, IMR: index of microvascular resistance.

TABLE 1

Studies comparing sensitivity and specificity in women and men

Noninvasive Test	Reference	Women		Men	
		Sensitivity	Specificity	Sensitivity	Specificity
Exercise Treadmill	Miller, et al 2002 (45)	0.30	0.82	0.42	0.78
Stress Echo					
Exercise Echo	Luotalahti, et al 1996(63)	0.77	0.80	0.96	0.60
Exercise Echo	Roger, et al 1997 (64)	0.79	0.37	0.78	0.44
Dobutamine Echo	Salustri et al 1992 (65)	0.83	0.75	0.48	0.86
Dobutamine Echo	Mazeika, et al, 1992 (66)	0.75	1.00	0.63	0.92
Dobutamine Echo	Marwick, et al, 1993(67)	0.55	0.75	0.75	0.88
Dobutamine Echo	Dionisopoulous, et al, 1997 (68)	0.90	0.79	0.85	0.96
Dobutamine Echo	Elhendy, et al, 1997 (69)	0.76	0.94	0.73	0.81
Dobutamine Echo	Seknus, et al 1997 (70)	0.78	0.55	0.88	0.46
Dobutamine Echo	Rollan, et al, 1999(71)	0.69	0.89	0.77	0.77
Myocardial Perfusion Imaging (MPI)					
Exercise MPI	Kiat et al, 1990 (72)	1.00	0.67	0.92	0.50
Exercise MPI	Van Train et al, 1990 (73)	0.95	0.62	0.95	0.43
Exercise and Vasodilator Stress	Gupta et al, 1992 (74)	0.85	0.67	0.81	0.86
Exercise and Vasodilator Stress	Sciammarella et al, 1992 (75)	1.00	0.40	0.95	0.33
Exercise and Vasodilator Stress	Hambye et al, 1996 (76)	0.61	0.67	0.94	0.82
Exercise and Vasodilator Stress	Astarita et al, 1998 (77)	1.00	0.47	1.0	0.50

J Nucl Cardiol. Author manuscript; available in PMC 2013 May 19.