

CONSENSUS STATEMENT

AMERICAN SOCIETY OF NUCLEAR CARDIOLOGY: TASK FORCE ON

WOMEN AND CORONARY ARTERY DISEASE.

THE ROLE OF MYOCARDIAL PERFUSION IMAGING IN THE CLINICAL

EVALUATION OF CORONARY ARTERY DISEASE IN WOMEN

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Preamble

The American Society of Nuclear Cardiology (ASNC), founded in 1993, is a professional medical society whose mission is to foster optimal delivery of nuclear cardiology services through professional education and leadership in the establishment of standards and guidelines for the practice of nuclear cardiology. ASNC will from time to time publish “Position, Policy or Consensus Statements”, which reflect a body of knowledge and clinical evidence for an application of radionuclide imaging techniques in the clinical care of patients with known or suspected heart disease. Position, Policy or Consensus Statements are approved by the ASNC Board of Directors prior to publication.

This Consensus Statement will examine the role of myocardial perfusion imaging studies in the diagnosis, risk assessment and treatment of women with known or suspected coronary artery disease.

Background

Cardiovascular disease is the leading cause of death of women in the United States. Despite advances in the diagnosis and management, coronary artery disease continues to claim the lives of greater than 230,000 American women each year (1). The lifetime risk of cardiovascular disease and its ensuing complications is 25% for a 40-year-old woman but increases to nearly 50% for older women (2). Prior to the last decade, under-representation of women in clinical trials and observational studies has led to a lack of available evidence and a generalized misperception that coronary artery disease was a “man’s disease” (3-11). As a result of a paucity of clinical evidence on diagnosis and treatment of coronary artery disease, the ensuing management patterns for women have been exceedingly inefficient. There is an abundance of evidence on under-recognition,

under-diagnosis and under-treatment of coronary disease in women contributing to higher cardiovascular mortality (3-11). Increased mortality has been repeatedly noted in women after myocardial infarction, where 38% of women as compared to 25% of men will die within one year after hospitalization (1). These data support a worse prognosis for women with coronary artery disease compared to men.

We believe that one key to affecting significant changes in cardiovascular mortality for women is the appropriate use of a highly accurate diagnostic test, such as gated myocardial perfusion SPECT, that results in early and effective treatment and improved outcome for at-risk women. The current document aims to put forth a synopsis of available evidence on the role of myocardial perfusion imaging studies in women.

Gender Differences in Noninvasive Diagnostic Testing for Coronary Artery Disease

There are several challenges for the noninvasive diagnosis of coronary artery disease in women. Under-representation of women in the major trials of coronary artery diagnosis has contributed to the paucity of gender specific data on the test performance characteristics and diagnostic accuracy of the most commonly used noninvasive tests. Since the 1990 congressional mandate that women be included in all federally funded cardiovascular trials, a growing body of data continues to support the fact that noninvasive cardiac tests have different diagnostic accuracy in women.

Several early reports have suggested that women are less often referred for invasive cardiac procedures even in the presence of multiple clinical variables or abnormal noninvasive tests (3-5). This reduced utilization of cardiac catheterization for women may in part be due to the lower pre and post testing noninvasive estimates of coronary artery disease. Although recent studies report on the absence of gender-related

differences in referral for coronary angiography controversy still exists as to the significance of gender bias in clinical practice (6-11).

Challenges in the Diagnosis of Coronary Artery disease with Exercise

Electrocardiography

Numerous reports have demonstrated a lower diagnostic accuracy of exercise electrocardiography in women, in particular the occurrence of ≥ 1 mm of ST segment depression (12-14). Average sensitivity and specificity for the exercise electrocardiogram are 61% and 69% (13-14).

The increased age of presentation by women, coincident with functional impairment, is associated with lower exercise capacity and an inability to attain maximal stress. Additional critical factors that have been reported to affect test accuracy in women include resting ST-T wave changes in hypertensive women, lower electrocardiographic voltage and hormonal factors (15-20). For the premenopausal woman, endogenous estrogen has a digoxin-like effect that may precipitate ST segment depression, resulting in a false positive test. (15). Physicians who test pre-menopausal women with chest pain or established coronary disease should caution the use of exercise stress testing in a woman's mid-cycle where estrogen levels are highest. Reports have noted a reduced frequency of ischemic episodes and chest pain during this phase of the menstrual cycle (16).

The accuracy of the exercise electrocardiogram in women, is highly variable and influenced by multiple factors including, exercise capacity and hormonal status. The current ACC/AHA guidelines for exercise testing recommend this test as a first line test for those with a normal resting 12-lead electrocardiogram and for those capable of

performing maximal stress (18). Although maximal stress may be defined by achieving $\geq 85\%$ of predicted maximal heart rate, care should be taken when interpreting a woman's heart rate response. For deconditioned patients, a hyperexaggerated response to physical work may result in marked increases in heart rate. Thus, the test should be continued until maximal symptom-limited exercise capacity. Women incapable of performing a minimum of 5 METS of exercise should be considered candidates for myocardial perfusion imaging with pharmacologic stress.

Women with diabetes are a special population worthy of mention. They are at an increased risk for premature atherosclerosis and at significant risk for myocardial infarction and cardiac death (1). The unique pathophysiology of diabetes mellitus makes traditional symptoms less reliable and diagnosis of coronary artery disease more challenging. The ECG is often a less reliable indicator of significant coronary artery disease in the diabetic patient (21). Myocardial perfusion imaging has been shown to be accurate in the risk assessment and prediction of future cardiac events in the diabetic woman. In a cohort of 2,086 women, stress myocardial perfusion imaging independently predicted future cardiac events in the 451 diabetic women enrolled in the study (22). The presence and extent of perfusion defects were the strongest predictor of future cardiac events among diabetic women. (22). Therefore, given the challenge of diagnosis of coronary artery disease in diabetic patients, myocardial perfusion imaging should be considered instead of exercise ECG in the diabetic women with suspected coronary artery disease.

A major key to the accurate diagnosis of coronary artery disease based upon the exercise electrocardiogram in women, is to include factors other than ST segment depression when interpreting the test (19-20). The integration of parameters such as the

Δ ST/heart rate index and the Duke treadmill score may improve diagnostic and prognostic accuracy of testing in women. (19-20). Women with a normal baseline ECG and an intermediate –high pretest likelihood of coronary artery disease should be considered for exercise combined with myocardial perfusion imaging, since myocardial perfusion imaging provides added diagnostic accuracy and incremental prognostic value in this group (14, 23).

Consensus: Exercise electrocardiography is useful in women with a good exercise capacity and with a normal baseline rest electrocardiogram (18). In the group of women with an intermediate –high pretest likelihood of coronary artery disease, combining exercise with myocardial perfusion imaging has added diagnostic and prognostic value over the exercise electrocardiogram (14, 23). For those women incapable of maximal exercise, those with diabetes, and those with an abnormal baseline electrocardiogram, myocardial perfusion imaging adds substantial incremental diagnostic and prognostic value over the exercise electrocardiogram (13, 22-27, 33,38).

Diagnosis of Coronary Artery Disease with Myocardial Perfusion Studies

A growing body of evidence supports the diagnostic value of stress myocardial perfusion imaging in the detection of coronary artery disease in women. Data have shown that stress myocardial perfusion imaging consistently has a significantly higher diagnostic accuracy than exercise testing alone (13, 28-33). In addition, exercise SPECT myocardial perfusion imaging is more accurate in diagnosing coronary artery disease than planar imaging (29). Limited data regarding diagnostic accuracy with pharmacologic stress imaging suggest improvement over exercise electrocardiography alone (30-32).

It is well appreciated that the diagnostic accuracy in women is adversely affected by gender specific factors such as breast attenuation, small left ventricular chamber size, and a high prevalence of single vessel coronary artery disease (29, 34). A study using thallium-201 imaging demonstrated a lower sensitivity for single vessel disease in women than men (25). This lower sensitivity for single vessel disease in women may be related to a generally small chamber size in female patients than in males (34). One study using Tc-99m sestamibi and pharmacologic stress has demonstrated a high sensitivity but a moderate specificity (32). The reduced specificity may be related to soft tissue attenuation from breast.

A recent meta analysis (21 studies with a total of 4,113 women) comparing exercise ECG, stress myocardial perfusion imaging and stress echocardiography also suggested a reduced specificity for myocardial perfusion imaging compared to echocardiographic techniques (14). However, the perfusion imaging studies included in that analysis incorporated substantial data from older literature, and no studies were included which incorporated contemporary imaging techniques such as gated SPECT imaging. Using gated SPECT, the simultaneously derived information on perfusion and function can assist in better differentiation of attenuation artifact from infarct.

In two recent studies involving over 170 women, gated SPECT imaging with Tc-99m sestamibi improved the previously reported specificity for detection of coronary artery disease in cohorts of women with suspected coronary artery disease (33, 36). The specificity in these two studies, 92 % and 91 %, were both higher than the upper limits of the confidence intervals on specificity in the meta-analysis of exercise ECG, perfusion imaging or echocardiographic studies(14, 33, 36). Therefore, contemporary myocardial perfusion imaging techniques with gated SPECT imaging using technetium99m-based

agents is of considerable importance in enhancing the diagnostic accuracy of myocardial perfusion imaging studies in women. These studies suggest that the specificity for ruling out disease when such techniques are used equals or possibly exceeds other techniques.

In summary, although some limitations are recognized, stress myocardial perfusion imaging plays an important role in the diagnosis of coronary artery disease in women and is clearly superior to exercise testing alone.

Consensus: Stress myocardial gated perfusion SPECT imaging is an effective non-invasive means of evaluating women with an intermediate –high pre test likelihood of suspected coronary artery disease.

Pharmacologic SPECT Myocardial Perfusion Imaging in Women:

Since, women are generally older when they present with coronary artery disease and have a higher incidence of decreased exercise capacity, many with known or suspected coronary artery disease are not able to complete a symptom-limited exercise protocol and are therefore candidates for pharmacologic stress testing. Approximately 40% of women who are referred for myocardial perfusion studies for the evaluation of known or suspected coronary artery disease are candidates for pharmacologic stress. While several studies have demonstrated a similar diagnostic accuracy of pharmacologic stress and exercise myocardial perfusion imaging, there are few data specific for women undergoing myocardial perfusion imaging with pharmacologic stressors of dipyridamole, adenosine or dobutamine(26, 27, 30-32).

Limited data comparing pharmacologic stress perfusion imaging to exercise electrocardiography support its higher diagnostic accuracy (13), although, it is

controversial as to which pharmacologic stress protocol is ideal for women with known or suspected coronary artery disease who are incapable of maximal stress with exercise. One study demonstrated a lower sensitivity of pharmacologic stress with thallium-201 in women compared to men, especially in the setting of one vessel disease. (25). The accuracy of pharmacologic stress with dipyridamole Tc-99m sestamibi SPECT was shown to be similar for detecting multivessel disease for men and women with a higher sensitivity for detecting disease of the left anterior descending coronary artery in women (33, 35). Pharmacologic stress with adenosine using a dual isotope SPECT protocol was shown to have a sensitivity of 93% specificity of 78% and diagnostic accuracy of 88% in a cohort of women with suspected coronary artery disease who underwent cardiac catheterization (30).

Consensus: Data thus far confirms the higher diagnostic accuracy of pharmacologic stress compared to exercise electrocardiography in the diagnosis of coronary artery disease in women. Pharmacologic stress myocardial perfusion imaging is recommended for the diagnosis of coronary artery disease in women with an intermediate-high pretest likelihood of coronary artery disease, who are incapable of achieving maximal stress with exercise.

The Role Of Myocardial Perfusion Imaging In The Risk Stratification of Women with Suspected Coronary Artery Disease

Myocardial perfusion imaging has been shown in a multitude of clinical investigations, which have included over 20,000 patients, to have powerful predictive value with regards to the development of subsequent cardiac events or need for

revascularization (22, 37-56). This prognostic value has also been documented specifically for women. Pooled data from over 7,500 women demonstrate an annual cardiac event rate of < 1% in the setting of a normal myocardial perfusion study (27, 37, 41-56)). Conversely, data from over 5, 000 women demonstrate a substantially increased risk for cardiac events if they have an abnormal perfusion study (26, 38, 40, 43,44, 46-54). Even when a high pretest likelihood of coronary disease is present, a very low cardiac event rate and performance of revascularization have been documented following a normal stress perfusion study (38). As the extent of the perfusion defect increases, so do the rates for both myocardial infarction and cardiac death (4-6 fold increase) (26, 38), and the odds ratio for an event with an abnormal scan has been found to be substantially higher for women than that seen for men (38).

Even when other clinical risk factors are present, the perfusion defect severity and extent independently predict future cardiovascular events (26, 38-40). An abnormal SPECT study is therefore independently valuable beyond any clinical or stress test parameter (26, 38-40). Myocardial perfusion imaging has also demonstrated prognostic value for women with regards to specific applications, such as in the assessment of peri-operative risk prior to major non-cardiac surgery (27).

Consensus: Based on a substantial body of evidence, including 3,402 women with chest pain in the Economics of Non-invasive Diagnosis multicenter registry of stable chest pain (26), myocardial perfusion imaging with exercise or pharmacologic stress is valuable and is recommended for the risk stratification of women with known or suspected coronary artery disease.

Recommendations For Myocardial Perfusion Imaging In Women

The early and accurate detection of flow-limiting coronary artery disease in women is of crucial importance in the selection of patients for referral for invasive procedures, coronary artery revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery. The diagnostic and prognostic value of stress myocardial perfusion imaging for the detection of coronary artery disease in women is firmly established. (57, 58). The use of gated SPECT imaging adds significantly to the diagnostic accuracy of imaging in women by improving specificity to >90%. Myocardial perfusion imaging in women adds incremental value to the use of clinical variables or exercise stress testing alone in the risk assessment of women with known or suspected coronary artery disease. Based on the clinical evidence, myocardial perfusion SPECT imaging with electrocardiographic gating, therefore, continues to be the cornerstone of the noninvasive evaluation of women with an intermediate pretest likelihood of coronary artery disease.

For these reasons, Table 1 details the appropriate candidates for referral to gated myocardial perfusion SPECT imaging. In general, the current evidence supports the use of gated myocardial perfusion SPECT imaging for symptomatic women who are at an intermediate pretest likelihood for coronary artery disease. Although the data are not as strong for women with a high pretest likelihood of coronary artery disease, myocardial perfusion imaging adds incremental prognostic value over resting ECG and clinical variables in this group. (38) Despite a high pretest likelihood of disease in women, a normal scan is associated with <1% cardiac event year over a 20 month period. (38).

Additional candidates for imaging include diabetic women (22) and those who should undergo pharmacologic stress because they are incapable of maximal exercise.

A recommended approach for the evaluation of women based upon the current clinical evidence is detailed in Figure 1.

Figure Legend

Figure 1. Recommended Algorithm for the Evaluation of Women with Suspected or Known Coronary Disease (57-58).

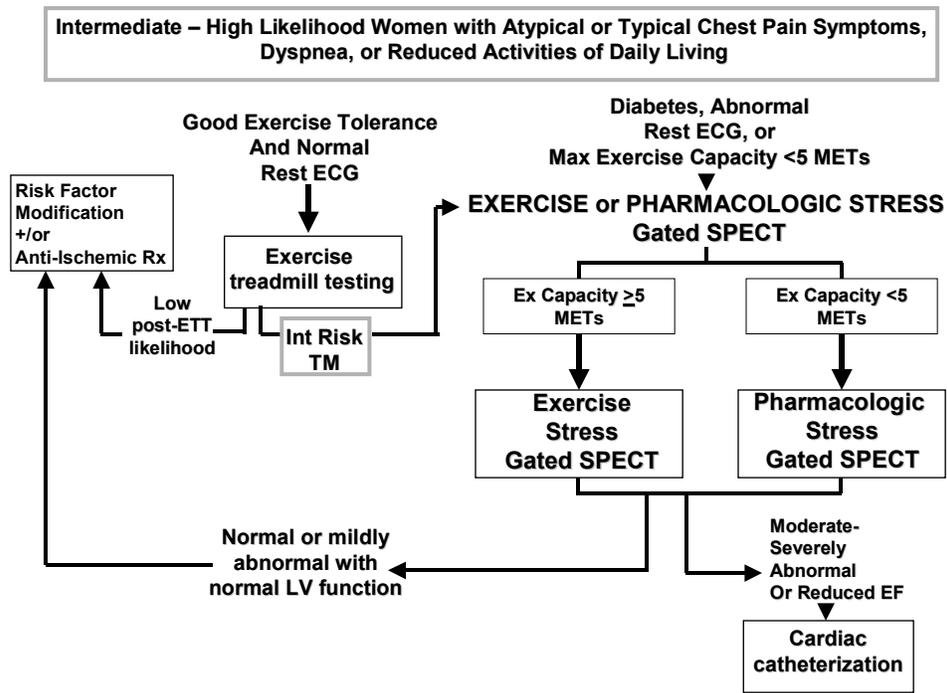


Table 1. Key Indications for Referral to Gated Myocardial Perfusion SPECT Imaging with Exercise or Pharmacologic Stress in Women: A Synthesis of the Supportive Evidence

	Key Indications	Supportive Evidence for Referral
Pretest Likelihood of Coronary Artery Disease	Intermediate-High Risk undergoing testing for symptom evaluation with the following: <ul style="list-style-type: none"> a. Abnormal Rest ECG, b. Poor Exercise Capacity (<5 METs), c. Intermediate Duke Treadmill Score, or Indeterminate Exercise Electrocardiogram 	1)ACC/AHA Guidelines for Exercise Testing and Stable Angina (18,58) 2) Effective Risk Stratification Using Exercise Myocardial Perfusion SPECT in Women: Gender-Related Differences in Prognostic Nuclear Testing. (38)
Special Populations		
Stable Chest Pain	Candidates for Pharmacologic Stress or Abnormal Rest ECG	ACC/AHA Guidelines for Stable Angina (58)
Diabetic Women	Preoperative Risk Assessment for Vascular Surgery, Kidney or Pancreas Transplant	Single Site and Multicenter Registry Data (22)

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