Women's Health Issues and Nuclear Medicine, Part I: Women and Heart Disease

April Mann

Nuclear Cardiology Laboratory, Hartford Hospital, Hartford, Connecticut

Objective: This is the first article of a four-part series on women's health issues and nuclear medicine. This article will review women and heart disease. After reading this article the technologist will be able to: (a) compare and contrast the differences in diagnosing coronary artery disease between men and women; (b) explain the importance of radionuclide myocardial perfusion imaging in diagnosing and stratifying risk of coronary artery disease in women; and (c) list and explain the technical challenges of imaging women's hearts.
Key Words: coronary artery disease; radionuclide myocardial perfusion imaging; technetium-99m-sestamibi; thallium-201

J Nucl Med Technol 1999; 27:89–92

Many Americans have the misconception that cardiovascular heart disease is a man's disease. In reality, cardiovascular heart disease is the single largest cause of death in American women (*1*). Cardiovascular disease claims the lives of more than 500,000 women annually, compared with all forms of cancer, which are responsible for the deaths of 250,000 women per year (*1*). Statistics have shown that 1 in 9 women between the ages of 45 and 64 y have some form of heart or blood vessel disease and this number increases to 1 in 3 women after age 65 (*1*). Since 1984, the total number of deaths due to cardiovascular disease in women annually has been greater than in men (*2*).

Distinct differences between coronary artery disease in men and in women have been recognized. Women average approximately 10 y older than men at the initial onset of coronary artery disease and are approximately 20 y older at the occurrence of myocardial infarction (*3*). This difference in age is thought to be due to the protective effects of estrogen in women. However, as women approach menopause their incidence of coronary artery disease increases and continues to do so with age.

Although women and men share similar cardiac risk factors, the profiles for men and women tend to differ. Women have a greater risk of developing hypertension at an earlier age, and by age 75 the prevalence is greater in women compared to men (*1*). Diabetes is more common among women than men at all ages. Although cholesterol levels are lower in women before menopause, after menopause their levels are higher compared to men at similar ages (*4,5*). Obesity, physical inactivity and tobacco use also have been associated with an increased risk of heart disease in women (*4,6,7*).

For correspondence or reprints contact: April Mann, CNMT, RT(N), Supervisor, Nuclear Cardiology Laboratory, Hartford Hospital, 80 Seymour St., Hartford, CT 06102.

DIAGNOSING CORONARY ARTERY DISEASE IN WOMEN

Diagnosing coronary artery disease in women continues to be a challenge for physicians. Women often experience symptoms that are different from men. Classic or typical symptoms for coronary artery disease have been based on what men experience and, until recently, the majority of research in coronary artery disease has been directed towards men (*8*).

Women more often than men experience chest pain as an initial symptom rather than myocardial infarction or cardiac death. Historically, however, chest pain has not been perceived to be of great prognostic value in women. This is based on follow-up reports from the Framingham study, which stated that although women develop symptoms more often than men, they progress less often to myocardial infarction (*3*). The Coronary Artery Surgery Study (CASS) found that of the 2810 women referred for coronary angiography for the evaluation of chest pain, 50% had no significant obstructive coronary artery disease (*9*).

Although chest pain is not considered to be of great prognostic value in women, it still remains the most common symptom reported by women with coronary artery disease. The Myocardial Infarction Triage and Intervention (MITI) Project reported that nearly 90% of women who suffered a myocardial infarction experienced chest pain as the initial symptom similar to men (*10*). It also reported, however, that women who suffered a myocardial infarction were significantly more likely than men to present with symptoms considered to be atypical, such as upper abdominal pain, dyspnea, nausea or fatigue.

Classifying the symptoms that women present with to angina, probable angina or nonspecific chest pain may help increase the prognostic value of these symptoms (*8*). Results of the CASS study showed that women with classical angina had a 71% chance of obstructive disease by coronary angiography

while those with probable angina had only a 36% chance of disease (*9*). Women who are considered to have nonspecific chest pain syndromes rarely are found to have any obstructive coronary artery disease by coronary angiography (*5*).

Health care professionals need to understand the differences in symptoms which women may present with and that symptoms, even those perceived to be atypical or possibly noncardiac in origin, should be evaluated with some type of diagnostic procedure. A recent review of the evaluation of chest pain syndromes in women suggested that it is possible to risk stratify women for coronary artery disease and use diagnostic procedures more informatively and effectively (*11*).

NONINVASIVE EVALUATION OF CORONARY ARTERY DISEASE IN WOMEN

Several noninvasive procedures have been studied to evaluate their role in diagnosing coronary artery disease in women including: cardiac fluoroscopy, exercise tolerance testing (ETT), exercise myocardial perfusion scintigraphy and stress echocardiography (*12–16*). Although exercise tolerance testing is the most commonly used procedure for evaluating chest pain syndromes, several studies have shown a lower sensitivity and specificity in women compared with men (*17–21*). This is probably due to the gender differences in the prevalence and extent of disease, as well as the inability of women to achieve an adequate heart rate response (*22*). Combined with exercise or pharmacologic stress testing, however, radionuclide myocardial perfusion imaging is considered to be one of the most important noninvasive modalities for detecting coronary artery disease in women.

RADIONUCLIDE MYOCARDIAL PERFUSION IMAGING

Exercise myocardial perfusion imaging has been reported to show increased sensitivity and specificity for detecting coronary artery disease over standard exercise treadmill testing alone for both men and women (*12,23–27*). There also has been an increase of sensitivity and specificity when performing SPECT myocardial perfusion imaging as compared to planar imaging (*28–29*).

As mentioned earlier, women are sometimes unable to achieve an adequate heart rate response with exercise testing alone. This may be due to the advanced age at which women experience the onset of symptoms, resulting in a diminished exercise capacity. For this reason, pharmacologic stress myocardial perfusion imaging has been found to be useful in women to achieve higher diagnostic accuracy than exercise testing alone (*30*).

Technical Challenges

One of the most common problems when performing SPECT myocardial perfusion imaging in women is a false-positive study due to breast attenuation artifact (*31–34*). This generally appears as a localized area of decreased photon activity because of the differential in counts due to attenuation and is most commonly seen as a fixed perfusion defect (Fig. 1). The artifacts vary in appearance because of differences in size, shape and density of breast tissue (*32*). Physicians always should review the unprocessed planar projection data before interpreting a SPECT study to identify breast attenuation.

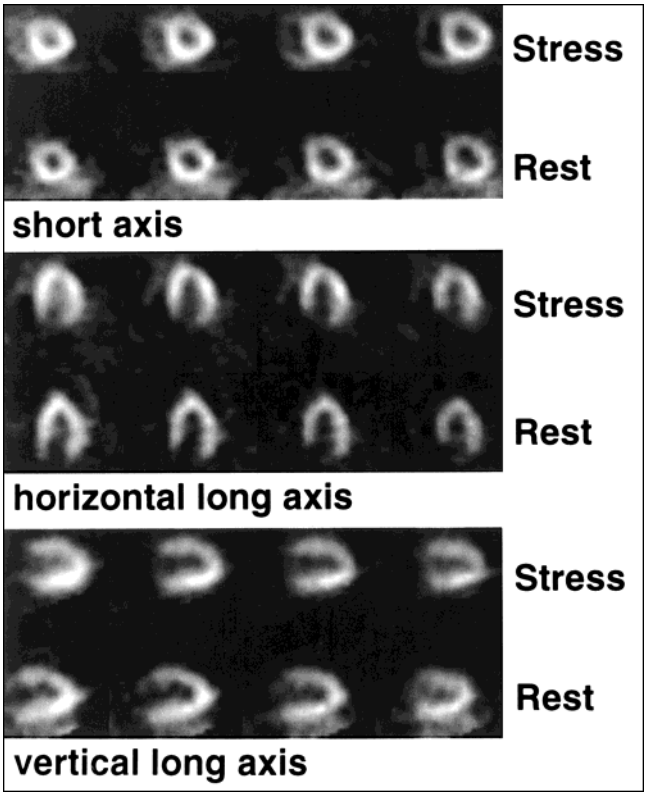

FIGURE 1. Breast attenuation artifact. The fixed area of decreased photon activity in the anterior wall visualized on the short- and horizontal long-axis images was caused by breast attenuation.

When performing myocardial perfusion imaging on women it is important to have similar positioning of the breast tissue for both the stress and rest acquisitions. It is recommended that women not wear brassieres during the acquisition because they may position the breast tissue more anteriorly and increase the amount of attenuation. However, if the patient wears a brassiere during the first acquisition, she should wear one during the second acquisition to maintain consistency.

Some laboratories use breast binders, which flatten the breast against the chest wall, or breast markers, which outline the breast tissue, to aide in recognizing and reducing breast attenuation artifacts. Both of these techniques may be helpful but require more precise and identical positioning of the breast during the stress and rest images, which may not always be possible (*32*).

Recent developments, such as ^{99m}Tc-labeled myocardial perfusion imaging agents as well as ECG gated SPECT imaging, have helped improve image quality and specificity when performing myocardial perfusion imaging in women (*35*). Technetium-99m-labeled agents offer a higher energy window (140 keV versus 80 keV) and shorter half-life (6 h versus 73 h) over ^{201}Tl. These characteristics result in a larger amount of activity administered for the same radiation exposure to the patient resulting in better count statistics. This increase in count statistics allows gated SPECT imaging to be performed. The

addition of gated SPECT imaging has improved the differentiation of scar versus attenuation artifacts when fixed defects are present and has increased diagnostic accuracy (*36*).

A study performed by Taillefer et al. directly compared the sensitivity and specificity of ^{201}Tl, ^{99m}Tc-sestamibi perfusion and ^{99m}Tc-sestamibi gated SPECT imaging for detecting coronary artery disease in women (*37*). They concluded that ^{201}Tl SPECT and ^{99m}Tc-sestamibi SPECT perfusion had similar sensitivities. However, ^{99m}Tc-sestamibi showed a significantly higher specificity, which was even further enhanced with gated SPECT imaging.

Attenuation correction is another proposed application that may offer assistance in the future for distinguishing between true perfusion defects and artifacts. This application has not been fully evaluated and will require more extensive clinical validation.

Other problems that may affect myocardial perfusion imaging in women are the high prevalence of single- versus multivessel disease in premenopausal women and the smaller chamber size of the left ventricle. These factors may have an effect on diagnostic accuracy (*12*,*29*,*30*,*38*,*39*).

Prognostic Value of Radionuclide Myocardial Perfusion Imaging

Myocardial perfusion imaging has been proven over the years to be a strong indicator of patient prognosis (*40*,*41*). Study results have reported a strong correlation between abnormal images and an increased risk of future cardiac events, while normal images have a low risk for future cardiac events. Although previous studies were performed on predominantly male populations, there have been several studies recently published evaluating the prognostic value of myocardial perfusion imaging in women (*42–45*). The results of these studies indicate that myocardial perfusion imaging is a strong predictor of patient prognosis in both genders (*35*).

CONCLUSION

Coronary artery disease is the number one cause of death in women in the U.S. Only recently has research been performed to evaluate the differences that exist among men and women with this disease. It has been established that women present with symptoms at an older age and their symptoms are often considered to be atypical in nature. This has made diagnosis in women more difficult.

Nuclear medicine has an important role in assisting with the diagnosis of coronary artery disease in women. Radionuclide myocardial perfusion imaging is considered one of the most important diagnostic procedures for women. It offers a high degree of diagnostic accuracy and is a strong indicator for patient prognosis. It is important for technologists to understand the differences between women and men to achieve optimal image quality for both genders.

REFERENCES

1. American Heart Association. *1997 Heart and Stroke Facts: Statistical Update*. Dallas, TX: American Heart Association; 1997.
2. American Heart Association. *About Women, Heart Disease and Stroke*. Dallas, TX: American Heart Association; 1998.
3. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J*. 1986; 111:383–390.
4. Rich-Edwards JW, Manson JE, Hennekens CH, et al. The primary prevention of coronary heart disease in women. *N Engl J Med.* 1995; 332:1758–1766.
5. Wenger NK. Coronary heart disease: diagnostic decision making. In: Douglas PS, ed. *Cardiovascular Health and Disease in Women*. Philadelphia, PA: WB Saunders Co; 1993: 25–42.
6. Eaker ED, Chesebro JH, Sacks FM, et al. Cardiovascular disease in women. *Circulation.* 1993; 88:1999–2009.
7. Willett WC, Green A, Stampfer MJ, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med.* 1987; 317:1303–1309.
8. Mosca L, Manson JE, Sutherland SE, et al. *Cardiovascular Disease in Women. A Statement for Healthcare Professionals from the American Heart Association*. Dallas, TX: American Heart Association; 1997.
9. Kennedy JW, Killip T, Fisher LD, et al. The clinical spectrum of coronary artery disease and its surgical and medical management 1974–1979. The Coronary Artery Surgery Study. *Circulation*. 1982; 66(5pt2):16–23.
10. Kudenchuk PJ, Maynard C, Martin JS, et al. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (the Myocardial Infarction Triage and Intervention Registry). *Am J Cardiol* 1996; 78:9–14.
11. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. *N Engl J Med.* 1996; 344:1311–1315.
12. Hung J, Chaitman BR, Lam J, et al. Noninvasive diagnostic test choices for the evaluation of coronary artery disease in women: a multivariate comparison of cardiac fluoroscopy, exercise electrocardiography and exercise thallium myocardial perfusion scintigraphy. *J Am Coll Cardiol.* 1984; 4:8–16.
13. Marwick TH, Anderson T, Williams MJ, et al. Exercise echocardiography is an accurate and cost-effective technique for detection of coronary artery disease in women. J *Am Coll Cardiol*. 1995; 26:335–341.
14. Williams MJ, Marwick TH, O'Gorman D, et al. Comparison of exercise echocardiography with an exercise score to diagnose coronary artery disease in women. *Am J Cardiol*. 1994; 74:435–438.
15. Marwick T, Willemart B, D'Hondt AM, et al. Selection of optimal nonexercise stress for evaluation of ischemic regional myocardial dysfunction and malperfusion. Comparison of dobutamine and adenosine using echocardiography and ^{99m}Tc-MIBI single photon emission computed tomography. *Circulation.* 1993; 87:345–354.
16. Marwick T, D'Hondt AM, Baudhuin T, et al. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy, or both? *J Am Coll Cardiol.* 1993; 22:159–167.
17. Sketch MH, Mohiuddin SM, Lynch JD, Zenka AE, Runco V. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. *Am J Cardiol.* 1975; 36:169–173.
18. Detry JM, Kapita BM, Cosyns J, et al. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary artery disease. *Circulation*. 1977; 56:756–761.
19. Weiner DA, Ryan TJ, McCabe CH, et al. Exercise stress testing. Correlations among history of angina, ST-segment response and the prevalence of coronary-artery disease in the Coronary Artery Surgery Study (CASS). *N Engl J Med*. 1979; 301:230–235.
20. Guiteras P, Chaitman BR, Waters DD, et al. Diagnostic accuracy of exercise ECG lead systems in clinical subsets of women. *Circulation*. 1982; 65:1465–1474.
21. Hlakty MA, Pryor DB, Harrell FE Jr., Califf RM, Rosati RA. Factors affecting sensitivity and specificity of exercise electrocardiography: multivariable analysis. *Am J Med.* 1984; 77:64–71.
22. Cerqueira MD. Diagnostic testing strategies for coronary artery disease: special issues related to gender. *Am J Cardiol.* 1995; 75:52D-60D.
23. Dash H, Massie BM, Botvinick EH, Brundage BH. The noninvasive identification of left main and three-vessel coronary artery disease by myocardial perfusion scintigraphy and treadmill exercise electrocardiography. *Circulation.* 1979; 60:276–284.
24. Pohost GM, Zir LM, Moore RH, et al. Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. *Circulation.* 1977; 55:294–302.

25. Okada RD, Boucher CA, Strauss HW, Pohost GM. Exercise radionuclide imaging approaches to coronary artery disease. *Am J Cardiol.* 1980; 46:1188–1204.
26. Brown KA, Boucher CA, Okada RD, et al. Prognostic value of exercise thallium-201 imaging in patients presenting for evaluation of chest pain. *J Am Coll Cardiol.* 1983; 1:994–1001.
27. Friedman TD, Greene AC, Iskandrian AS, et al. Exercise thallium-201 myocardial scintigraphy in women: correlation with coronary arteriography. *Am J Cardiol.* 1982; 49:1632–1637.
28. Fintel DJ, Links JM, Brinker JA, et al. Improved diagnostic performance of exercise thallium-201 single photon emission computed tomography over planar imaging in the diagnosis of coronary artery disease: a receiver operating characteristic analysis. *J Am Coll Cardiol.* 1989; 13:600–612.
29. Chae SC, Heo J, Iskandrian AS, et al. Identification of extensive coronary artery disease in women by exercise single-photon emission computed tomography (SPECT) thallium imaging. *J Am Coll Cardiol.* 1993; 21:1305–1311.
30. Amanullah AM, Kiat H, Friedman JD, et al. Adenosine technetium-99m sestamibi myocardial perfusion SPECT in women: diagnostic efficacy in detection of coronary artery disease. *J Am Coll Cardiol.* 1996; 27:803–809.
31. Goodgold HM, Rehder JG, Samuels LD, et al. Improved interpretation of exercise Tl-201 myocardial perfusion scintigraphy in women: characterization of breast attenuation artifacts. *Radiology.* 1987; 165:361–366.
32. DePuey EG. Artifacts in SPECT myocardial perfusion imaging. In: DePuey EG, Berman DS, Garcia EV, eds. *Cardiac SPECT Imaging*. New York, NY: Raven Press; 1995: 169–200.
33. Wackers F. Diagnostic pitfalls of myocardial perfusion imaging women. *J Myocardial Ischemia.* 1992; 10:23–37.
34. Dunn RF, Wolff L, Wagner S, et al. The inconsistent pattern of thallium defects: a clue to the false positive perfusion scintigram. *Am J Cardiol.* 1981; 48:224–232.
35. Miller DD. Optimal imaging approaches for the evaluation of chest pain syndromes in women. *Cardiol in Review.* 1997; 5:279–284.
36. DePuey EG, Rozanski A. Using gated technetium-99m-sestamibi SPECT to characterize fixed myocardial defects as infarct or artifact. *J Nucl Med.* 1995; 36:952–955.
37. Taillefer R, DePuey EG, Udelson JE, et al. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. *J Am Coll Cardiol.* 1997; 29:69–77.
38. Welch CC, Proudfit WL, Sheldon WC. Coronary arteriographic findings in 1,000 women under age 50. *Am J Cardiol.* 1975; 35:211–215.
39. Hansen CL, Crabbe D, Rubin S. Lower diagnostic accuracy of thallium-201 SPECT myocardial perfusion imaging in women: an effect of smaller chamber size. *J Am Coll Cardiol.* 1996; 28:1214–1219.
40. Heller GV, Brown KA. Prognosis of acute and chronic coronary artery disease by myocardial perfusion imaging. *Cardiol Clin.* 1994; 12:271–287.
41. Pattillo RW, Fuchs S, Johnson J, et al. Predictors of prognosis by quantitative assessment of coronary angiography, single photon emission computed tomography thallium imaging, and treadmill exercise testing. *Am Heart J.* 1996; 131:582–590.
42. Pancholy SB, Fattah AA, Kamal AM, et al. Independent and incremental prognostic value of exercise thallium single-photon emission computed tomographic imaging in women. *J Nucl Cardiol.* 1995; 2:110–116.
43. Shaw LJ, Miller DD, Romeis JC, et al. Gender differences in the noninvasive evaluation and management of patients with suspected coronary artery disease. *Ann Intern Med.* 1994; 120:559–566.
44. Hachamovitch R, Berman DS, Kiat H, et al. Gender-related differences in clinical management after exercise nuclear testing. *J Am Coll Cardiol.* 1995; 26:1457–1464.
45. Travin MI, Duca MD, Kline GM, et al. Relation of gender to physician use of test results and to the prognostic value of stress technetium 99m sestamibi myocardial single-photon emission computed tomography scintigraphy. *Am Heart J.* 1997; 134:73–82.