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Prognosis of a Normal Positron Emission Tomography ^{82}Rb Myocardial Perfusion Imaging Study in Women with No History of Coronary Disease

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Key Words
Prognosis · Women · Myocardial perfusion imaging · Positron emission tomography imaging

Abstract
Objectives: Myocardial perfusion imaging (MPI) with positron emission tomography (PET) has advantages over single-photon emission computerized tomography, particularly for women. This investigation was undertaken to define the prognosis of a normal stress PET MPI study in women. ***Methods:*** The cohort comprised 457 women evaluated for suspected coronary artery disease (CAD) who had normal pharmacologic stress ^{82}Rb PET MPI. No patient had clinically evident CAD. Kaplan-Meier estimates were used to determine death and initial nonfatal cardiac event rates over 7 years. Log rank tests were used to assess the relationship between baseline cardiac risk and events during follow-up, and to contrast survival in the cohort with age- and gender-matched US census comparators. ***Results:*** During follow-up, there were 11 deaths (all nonischemic), 3 nonfatal myocardial infarctions, 3 percutaneous coronary interventions and 1 coronary artery bypass operation. Average risks of death and initial nonfatal cardiac events were 0.72 and 0.47% per year, respectively. Cardiac events were associated with a history of diabetes ($p < 0.0003$) and a family history of CAD ($p < 0.05$). ***Conclusion:*** A normal cardiac PET study is associated with a very low rate of future cardiac events. Women with diabetes and a strong family history of CAD are more likely to sustain events and require close surveillance for the development of coronary disease.

Introduction

Coronary artery disease (CAD) has become the leading cause of mortality in women in the USA, accounting for 220,000 deaths per year [1, 2]. CAD deaths in women now outnumber those in men, and 38.2 million women in the USA are estimated to have CAD [1–3]. Thus, the accurate diagnosis of CAD in women has become increasingly important, but may be more clinically difficult to achieve than in men. Chest pain and the clinical presentation of CAD in women are often atypical [1, 4], and routine diagnostic tests, such as stress electrocardiography, may be associated with a high incidence of false-positive findings [4, 5]. Stress myocardial perfu-

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sion imaging (MPI) using ^{201}Tl in women report a significant incidence of false-positive results due to variable soft tissue (breast) attenuation [6–9]. MPI studies using technetium isotopes, quantification and gated single-photon emission computerized tomography (SPECT) wall motion studies achieve higher sensitivities, specificities and normalcy rates. However, variable breast attenuation and smaller heart size in women still pose problems for the clinical interpretation of MPI, and may result in reductions in both specificity *and* sensitivity [10–13]. The optimum method to diagnose women at risk for cardiac events remains a subject of investigation [14].

Although women with normal SPECT studies have a low cardiac event rate (<0.7%) [15–17], limitations of conventional noninvasive diagnostic tests may lead to studies that are equivocal or nondiagnostic [12]. Compared to SPECT, positron emission tomography (PET) has potential advantages for performing stress MPI in women, including superior spatial resolution and validated attenuation correction [18, 19]. In women who have had noninvasive studies that are either nondiagnostic or suspected of being false positive due to attenuation, a subsequent normal PET study may indicate normal myocardial perfusion and an excellent long-term prognosis, obviating the need for invasive contrast-based imaging [20]. However, few data are available on the prognostic value of a normal PET scan in women [21], nor has any study specifically examined the prognosis of a normal PET study in women without prior history of coronary disease [21, 22].

The purpose of this investigation was to further define the prognosis of a normal stress PET MPI in women. We focused on a cohort with no preceding history of clinically evident CAD, so that our data would be applicable to the typical patient who presents for evaluation of chest pain or suspected CAD. Our hypothesis was that in this group, a normal PET MPI would effectively rule out prognostically important CAD and eliminate the need for further invasive cardiac studies.

Methods

The study was approved by the Committee on Scientific Activities of Beth Israel Medical Center, New York, N.Y., USA. Informed consent was obtained from all subjects, or from next of kin for patients who had died during follow-up.

Patient Selection

The sample was drawn from a consecutive series of women who underwent pharmacologic stress PET MPI for the indications of chest discomfort, investigation of symptoms presumed to be an angina equivalent, or to otherwise evaluate suspected CAD. All tests were performed at Beth Israel Medical Center, New York, from November 1995 to December 1998. The study cohort included all female patients who met the following criteria: (1) no history, prior to PET imaging, of myocardial infarction (MI), percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG); (2) for any patient who had coronary angiography performed prior to PET imaging, no major coronary artery or branch vessel with >50% stenosis; (3) rest and stress ^{82}Rb PET perfusion imaging interpreted as normal, with no perfusion defects on either set of images, by qualitative interpretation performed by an experienced reader, and (4) willingness to participate in a clinical follow-up assessment.

There were 579 women who had a normal PET during the period outlined above. Eighty-one patients were excluded because of a prior history of documented CAD (as defined above). There were 41 patients who were excluded because of refusal to participate in the study, uncertainty regarding the presence of preexisting CAD or lack of follow-up after the index PET. The remaining 457 patients (92% of total eligible patients) comprise the cohort in the present analysis.

Pharmacologic Stress ^{82}Rb PET MPI

Pharmacologic stress testing was performed using dipyridamole, or dobutamine in the small minority of patients with reactive airways disease [23]. Stress testing procedures, including patient preparation, duration of fasting, abstention from caffeine and withholding of cardiac medications, conformed to accepted standard protocols [24]. Blood pressure, heart rate and cardiac rhythm were monitored throughout. At rest, an activity of 1.48–1.65 GBq (40–50 mCi) of ^{82}Rb was infused over 20–30 s from a strontium-rubidium generator (Bracco Diagnostics Inc., Princeton, N.J., USA), which measured the delivered dose using a beta probe [25]. At peak pharmacologic stress (8 min after dipyridamole injection, or at peak heart rate during dobutamine testing), an identical activity of isotope to that used for rest imaging was infused and stress images were acquired. PET imaging was performed as previously reported [26, 27], using a Posicam PET camera (Positron, Houston, Tex., USA), a 21-slice bismuth germanate oxide system with an 11.5-cm field of view and 5.0-mm in-plane intrinsic resolution. Transmission scans for attenuation correction used a ^{68}Ge line source and a fan beam rejection method for minimizing random counts [28]. Perfusion imaging was performed in profile mode. A 6-min static acquisition was begun 70 s after the infusion of isotope to allow for clearance of blood pool activity. Image data were reconstructed into transaxial tomograms using algorithms providing 10- to 12-mm axial resolution for the heart (Butterworth filter, cutoff 0.4, order 5.0, z-axis smoothing). Transaxial images were reoriented into standard vertical and horizontal long-axis and short-axis tomograms. Standard polar coordinate maps were constructed from the short-axis data with counts normalized to peak myocardial values.

Image Interpretation

A nuclear cardiologist with extensive experience in cardiac PET imaging qualitatively reviewed the ungated rest and stress vertical and horizontal long-axis and short-axis tomograms simultaneously for the presence of perfusion defects. A conventional 17-segment left ventricle model was used [29], and segmental

perfusion was graded on a 4-point scale (0 = normal, 1 = mild perfusion defect, 2 = moderate perfusion defect, 3 = severely reduced ^{82}Rb uptake). All patients in this study had been judged to have completely normal myocardial perfusion (equivalent to a summed stress score of 0) in all segments, for both rest and stress imaging, on the original clinical report. The studies were not reinterpreted retrospectively for the purpose of this investigation.

Assessment of Baseline Risk Factors and Events during Follow-Up

Demographics, clinical history and coronary risk factors (diabetes, hypertension, hypercholesterolemia, family history of CAD and smoking history) were evaluated at the time of the index PET study. Events during follow-up (death, nonfatal MI, PCI or CABG) were determined by telephone and/or postal mail contact with the patient (or a family member or caregiver, if the patient could not be contacted) and the patient's physician and were confirmed by review of medical and vital records. The services of Pension Benefits Information, San Rafael, Calif., USA, were enlisted to locate patients who were lost to follow-up, to verify deaths among this subgroup and to assist in the procurement of death certificates. Cardiac events were defined, and deaths were classified as cardiac (ischemic or nonischemic) versus noncardiac, using accepted standards [30].

Statistical Analysis

Summary statistics are presented as mean ± standard deviation or number and percentage, as appropriate. The Kaplan-Meier product limit estimate method was used to define the time from the index PET study to (1) death (all causes) and (2) initial nonfatal ischemic events (MI, PCI or CABG) during follow-up among members of the cohort. Univariable Cox model analysis and log rank test comparisons of Kaplan-Meier curves were used to determine the impact of age and coronary risk factors (evaluated individually and as total number of risk factors per patient) on the time to cardiac events among the cohort. Multivariable analysis was not performed due to low event rates. The rates of death (all-cause mortality) among members of the cohort were compared to those of age-matched women drawn from US census data using the one-sample log rank test [31]. Probability (p) values <0.05 (2-tailed test) were considered significant.

Results

Patient Characteristics

The study group comprised 457 women, mean age 63 ± 12 years (range 29–90 years). Their average number of major cardiac risk factors (diabetes, elevated cholesterol, cigarette smoking within the last 10 years, hypertension or family history of CAD prior to age 55) was 1.7 ± 1.2 (table 1).

Table 1. Clinical characteristics of the patient population (n = 457)

Variable	n (%)
History of diabetes mellitus	65/452 (14.2)
History of hypercholesteremia	193/452 (42.3)
History of hypertension	221/452 (48.3)
Family history of CAD[1]	196/452 (42.9)
Cigarette smoking (current or in last 10 years)	80/452 (17.5)
CAD risk factors[2]	92/452 (20.4)
1 CAD risk factor	115/452 (25.4)
2 CAD risk factors	131/452 (29.0)
3 CAD risk factors	86/452 (19.0)
4 CAD risk factors	26/452 (5.8)
5 CAD risk factors	2/452 (0.4)
Average number of CAD risk factors[2] (range)	1.66 ± 1.19 (0–5)
Average age at index PET study, years (range)	62.63 ± 12.02 (26.6–90.3)

[1] MI or angina before age 55.

[2] CAD risk factors: history of diabetes mellitus, history of hypercholesteremia, history of hypertension, family history of CAD, current smoker or smoked in last 10 years.

Cardiac Events during Follow-Up

During an average follow-up of 3.3 ± 1.6 years (range 0.2–7.2 years), there were 11 deaths, including 9 noncardiac deaths and 2 cardiac deaths (the latter due to heart failure in the setting of nonischemic cardiomyopathy). The average annual mortality risk (AAR) in the cohort was 0.72% (fig. 1). There were no ischemic cardiac deaths. Survival among the normal PET cohort was significantly ($p < 0.002$) better than survival of age- and gender-matched US census comparators.

There were 7 nonfatal ischemic cardiac events (3 nonfatal MIs, 3 PCIs and 1 CABG). The AAR of nonfatal MI was 0.2%, and for coronary intervention (PCI or CABG) it was 0.27%; the AAR of total nonfatal ischemic cardiac events was 0.47% (fig. 2).

Evaluation of the time course of ischemic cardiac events indicated that none occurred during the first year after PET imaging was performed. There was one event, a CABG, that occurred between years 1 and 2. The balance of ischemic events (3 nonfatal MIs and 3 PCIs) occurred between years 3 and 5 of follow-up.

A significant association was observed between the incidence of ischemic cardiac events and the presence of diabetes ($p < 0.0003$) and family history of CAD at baseline ($p < 0.05$). The association of cardiac events with hypercholesterolemia ($p < 0.06$) and hypertension ($p < 0.09$) was weaker and did not reach statistical significance.

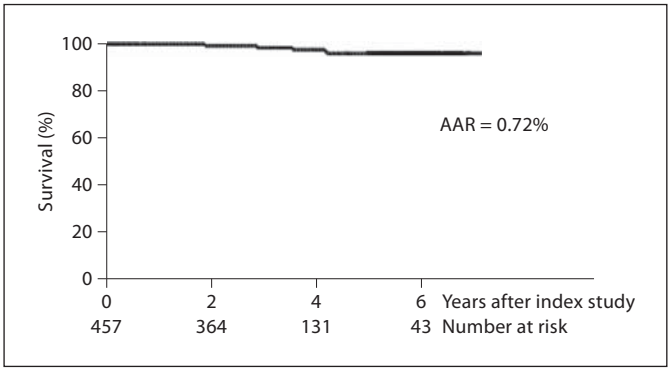

Fig. 1. Percent survival (freedom from all-cause mortality) among 457 female patients evaluated for suspected CAD who had normal pharmacologic stress ^{82}Rb PET MPI.

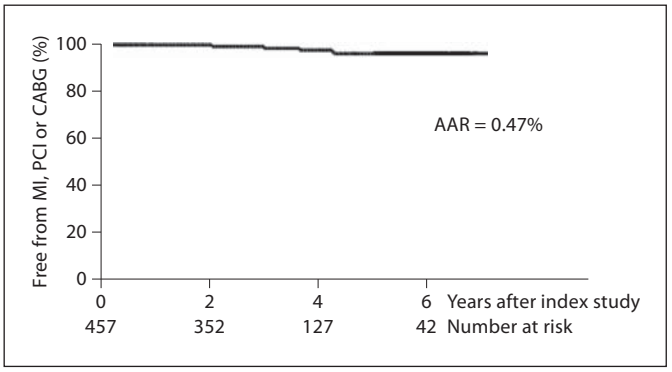

Fig. 2. Percentage of patients free from nonfatal ischemic cardiac events (MI, PCI or CABG) among 457 female patients evaluated for suspected CAD who had normal pharmacologic stress ^{82}Rb PET MPI.

Discussion

Our study confirms a very low event rate for women with significant cardiac risk factors suspected of having CAD who have a normal stress PET MPI study. No ischemic cardiac deaths were identified. In the first 2 years of follow-up, only 1 ischemic cardiac event was reported, a CABG, suggesting a 'warranty period' of 18–24 months for a normal PET study in this selected population. In our cohort of women with a normal PET, the risk of future fatal events was lower than in an age- and gender-matched general population, despite the high prevalence of risk factors in our cohort (14% diabetes, 42% hypercholesterolemia, 48% hypertension), which might be expected to yield a greater future event rate than the general population.

PET Imaging Advantages for Women

^{82}Rb PET has technical advantages over SPECT, including higher scanner sensitivity and better spatial resolution [18], which may enhance detection of perfusion defects in women, whose small ventricular chambers may cause false-negative scans [11]. PET's attenuation correction mitigates artifacts that cause false positives and reduce specificity [18]. Soft tissue artifacts may also reduce sensitivity, as readers disregard true perfusion defects to compensate for attenuation [13]. PET achieves higher sensitivity and specificity compared to SPECT [32, 33].

Prognosis of a Normal PET Myocardial Perfusion Scan

A normal SPECT MPI confers a good prognosis [16], with cardiac event rates of 0.6–1.6% per year for all patients, depending on the characteristics of the population being studied and the definition of events. Women with normal SPECT MPI have event rates of 0.7–1.3% per year [15, 17, 34].

To date, there have been no studies specifically defining the prognosis of normal ^{82}Rb PET in women. Several reports do provide data on the prognosis of all patients with normal cardiac PET MPI. Those investigations differ with regard to the pretest cardiac risk of their patient populations and their analysis of the effect of gender on prognosis. Marwick et al. [35] studied 685 patients (29% women), 70% of whom had known CAD. Cardiac mortality was 0.9% per year in patients with normal scans, with no statistical effect of gender on prognosis, but results in women with normal scans were not reported. Yoshinaga et al. [36] followed 367 patients (54.2% women) who had ^{82}Rb PET MPI, 40% of whom had known CAD. Patients with a normal PET had an overall event rate of 1.7% (including cardiac hospitalizations), with an event rate of 0.4% for nonfatal MI and cardiac death. Events were said to be less frequent for women than men. Ninety patients had PET following abnormal or equivocal SPECT MPI. The event rate was 1.3% per year in patients with normal PET versus 15.2% per year in those with abnormal scans. The authors concluded that PET could be used to further define coronary risk following nondiagnostic noninvasive studies.

Chow et al. [21] performed ^{82}Rb PET in 694 patients, 25% of whom had confirmed CAD. The event rate in patients with normal scans was 0.98% per year for cardiac death, MI or revascularization. Event rates were not reported by gender, but were said not to differ between men and women. Dorbala et al. [37] reported on 1,432 patients (52% female) with ^{82}Rb PET, 30% of whom had known CAD (mean follow-up of 1.7 years). The event rate in pa-

tients with normal scans was 1.2% per year, but it was not analyzed by gender. Lertsburapa et al. [38] studied 1,441 patients (58% women), 53% with known CAD (mean follow-up of 2.5 years). Mortality was 2.1% in patients with normal scans and was associated with increased age and diabetes but not gender.

In prior studies, the prevalence of known CAD was 25–70%, associated with a 0.9–2.1% event rate, versus 0% prevalence and a 0.47% event rate in the current study [21, 35–38]. The higher event rates in previous studies are likely due to progression of more extensive underlying CAD [21, 35–38]. The event rates we found are less influenced by progression of preexisting CAD and thus more indicative of the ability of PET to identify women with no or minimal ischemia. A normal ^{82}Rb PET cannot entirely exclude the presence of early CAD, which may suddenly worsen due to plaque rupture [39]. The correlation we noted between ischemic events following PET imaging and diabetes is consistent with the known association of this risk factor with abrupt CAD progression [40, 41].

Clinical Implications

In women being evaluated for chest pain or suspected CAD, false-positive or nondiagnostic noninvasive studies are common and may lead to the performance of a second diagnostic test [36]. Our data suggest that a normal ^{82}Rb PET MPI in women is associated with a very low rate of ischemic events over an average 3.3-year follow-up. PET MPI has the potential to substitute for more invasive cardiac diagnostic studies [36]. Our data confirm the association of diabetes with future ischemic events following a normal perfusion scan [41], supporting the recommendation for a 2-year screening interval for diabetics [42].

Study Limitations

Ours was a single-center study, with images interpreted by a reader highly experienced in PET MPI, and thus may not be applicable to all institutions. While appreciable efforts were made to obtain data on all candidates who were potentially suitable for the study, the lack of complete participation from all eligible patients may have led to an underestimation of even rates. The 92% rate of participation achieved in our study exceeds that of other prognostic studies of PET MPI (90.6% [21] and 84.3% [36]). Patients in our study had an average of 1–2 coronary risk factors, suggesting they were in a low-to-intermediate-risk group, but data on the specific pretest likelihood of CAD for each patient were not available. Although we found a correlation between cardiac events, diabetes and a family history of CAD, the precise relationship between the pretest likelihood of CAD and future cardiac events could not be evaluated.

Attenuation correction for this study was performed using a ^{68}Ge line source. Attenuation correction can also be achieved using CT, enabling calcium scoring and quantitation of absolute perfusion [18, 43, 44], which may have identified patients whose scans appeared qualitatively normal but who had early nonobstructive CAD or balanced ischemia. However, CT has a higher prevalence of misregistration artifacts than scanning line source technology [43].

Conclusion

PET MPI is a highly effective methodology to evaluate women with chest pain or suspected CAD and obtain prognostically important clinical information. A normal PET scan in this population is associated with a very low coronary event rate, particularly in the first 1–2 years, suggesting that PET is highly specific in excluding significant coronary disease. Women with risk factors, particularly diabetes and a strong family history of CAD, are more likely to sustain coronary events after the first year and require close surveillance for the development of coronary disease.

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References

1 Mosca L, Banka CL, Benjamin EJ, et al: Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. Circulation 2007;115:1481–1501.

2 Rosamond W, Flegal K, Friday G, et al: Heart disease and stroke statistics – 2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2007;115:e69–e171.

3 Heron M, Hoyert DL, Murphy SL, Kochanek KD: National Vital Statistics Report. Deaths: Final Data for 2006. Hyattsville, US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, 2009.

4 Douglas PS, Ginsburg GS: The evaluation of chest pain in women. N Engl J Med 1996;334:1311–1315.

5 Kwok Y, Kim C, Grady D, Segal M, Redberg R: Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol 1999;83:660–668.

6 Weiner DA, Ryan TJ, McCabe CH, et al: Exercise stress testing. Correlations among history of angina, ST-segment response and prevalence of coronary artery disease in the Coronary Artery Surgery Study (CASS). N Engl J Med 1979;301:230–235.

7 Taillefer R, Depuey G, Udelson JE, Beller GA, Latour Y, Reeves F: 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.

8 Beller GA, Zaret BL: Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. Circulation 2000;101:1465–1478.

9 Rozanski A: Proceed with caution: reliance on coronary angiography to exclude organic disease in women. J Nucl Cardiol 2006;13: 450–456.

10 Manglos SH, Thomas FD, Gange GM, Hellwig BJ: Phantom study of breast tissue attenuation in myocardial imaging. J Nucl Med 1993;34:992–996.

11 Hansen CL, Crabbe D, Rubin S: Lower diagnostic accuracy of thallium-201 SPECT myocardial perfusion imaging in women: an effect of smaller chamber. J Am Coll Cardiol 1996;28:1214–1219.

12 Iskandrian AE, Heo J, Nallamothu N: Detection of coronary artery disease in women with use of stress single-photon emission computed tomography myocardial perfusion imaging. J Nucl Cardiol 1997;4:329–335.

13 Heller GV: Attenuation artifact in radionuclide myocardial perfusion imaging. Uptodate On Line. 2010. http://www.uptodate.com/patients/content/topic.do?topicKey=~shpFoiH.gs.

14 Mieres JH, Shaw LJ, Hendel RC, Heller GV: The WOMEN Study: what is the optimal method for ischemia evaluation in women? A multi-center, prospective, randomized study to establish the optimal method for detection of coronary artery disease risk in women at an intermediate-high pre-test likelihood of CAD: study design. J Nucl Card 2009;16:105–112.

15 Berman DS, Kang X, Hayes SW, et al: Adenosine myocardial perfusion single-photon emission computed tomography in women compared with men. Impact of diabetes mellitus on incremental prognostic value and effect on patient management. J Am Coll Cardiol 2003;41:1125–1133.

16 Klocke FJ, Baird MG, Lorell BH, et al: ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging – executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). Circulation 2003; 108:1404–1418.

17 America YGCJ, Bax JJ, Boersma E, Stokkel M, van der Wall E: The additive prognostic value of perfusion and functional data assessed by quantitative gated SPECT in women. J Nucl Cardiol 2009;16:10–19.

18 Di Carli MF, Hachamovitch R: New technology for noninvasive evaluation of coronary artery disease. Circulation 2007;115:1464–1480.

19 Knuuti J, Bengel FM: Positron emission tomography and molecular imaging. Heart 2008;94:360–367.

20 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.

21 Chow BJ, Wong JW, Yoshinaga K, et al: Prognostic significance of dipyridamole-induced ST depression in patients with normal ^{82}Rb PET myocardial perfusion imaging. J Nucl Med 2005;46:1095–1101.

22 Shaw LJ, Buriardini R, Merz CNB: Women and ischemic heart disease: evolving knowledge. J Am Coll Cardiol 2009;54:1561–1575

23 Botvinick EH: Current methods of pharmacologic stress testing and the potential advantages of new agents. J Nucl Med Technol 2009;37:14–25.

24 Henzlova MJ, Cerquiera MD, Hansen CL, Taillefer R, Yao SS: ASNC Imaging Guidelines for Nuclear Cardiology Procedures: stress protocols and tracers. 2009. http://www.asnc.org/imageuploads/ImagingGuidelinesStressProtocols021109.pdf, 2009.

25 Gould KL: Clinical cardiac PET using generator-produced Rb-82: a review. Cardiovasc Intervent Radiol 1989;12:245–251.

26 Van Tosh A, Garza D, Roberti R, et al: Serial myocardial perfusion imaging with dipyridamole and rubidium-82 to assess restenosis after angioplasty. J Nucl Med 1995;36:1553–1560.

27 Garza D, Van Tosh A, Roberti R, et al: Detection of coronary collaterals using dipyridamole PET myocardial perfusion imaging with rubidium-82. J Nucl Med 1997;38:39–43.

28 Bailey DL: Transmission scanning in emission tomography. Eur J Nucl Med 1998;25: 774–787.

29 Holly TA, Abbott BG, Al-Mallah M, et al: ASNC Imaging Guidelines for Nuclear Cardiology Procedures: single photon emission computed tomography. http://www.asnc.org.

30 Battler A, Brindis R, Cox JL, et al: American College of Cardiology key data elements and definitions for measuring outcomes of patients with acute coronary syndromes. J Am Coll Cardiol 2001;38:2114–2130.

31 Therneau TM, Sicks JD, Bergstralh EJ, Offord J: Expected Survival Based on Hazard Rates. Mayo Clinic Technical Report Series, No 52. Rochester, Mayo Foundation, 1994.

32 Bateman TM, Heller GV, McGhie I, et al: Diagnostic accuracy of rest/stress ECG-gated Rb-82. J Nucl Cardiol 2006;13:24–33.

33 Machac J: Cardiac positron emission tomography imaging. Semin Nucl Med 2005;35: 17–36.

34 Amanullah AM, Berman DS, Erel J, et al: Incremental prognostic value of adenosine myocardial perfusion single-photon emission computed tomography in women with suspected coronary artery disease. Am J Cardiol 1998;82:725–730.

35 Marwick TH, Shan K, Patel S, Go RT, Lauer MS: Incremental value of rubidium-82 positron emission tomography for prognostic assessment of known or suspected coronary artery disease. Am J Cardiol 1997;80:865–870.

36 Yoshinaga K, Chow BJ, Williams K, et al: What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? J Am Coll Cardiol 2006;48:1029–1039.

37 Dorbala S, Hachamovitch R, Curillova Z, et al: Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. JACC Cardiovasc Imaging 2009;2:846–854.

38 Lertsburapa K, Ahlberg AW, Bateman TM, et al: Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium-82 PET imaging in patient with known or suspected coronary disease. J Nucl Card 2008;15:745–753.

39 Ambrose JA, Tannenbaum MA, Alexopoulos D, et al: Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56–62.

40 Nesto RW: Diabetes and heart disease; in Libby P (ed): Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. New York, Saunders, 2007, pp 1552–1554.

41 Giri S, Shaw LJ, Murthy DR, et al: Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. Circulation 2002;105:32–40.

42 Hendel RC, Berman DS, Di Carli MF, et al: ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate use criteria for cardiac radionuclide imaging: a Rrport of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. J Am Coll Cardiol 2009;53:2201–2229.

43 Le Meunier L, Maass-Moreno R, Carrasquillo JA, Dieckmann W, Bacharach SL: PET/CT imaging: effect of respiratory motion on apparent myocardial uptake. J Nucl Card 2006; 13:821–830.

44 Gould KL: Does coronary flow trump coronary anatomy? JACC Cardiovasc Imaging 2009;2:1009–1023.