

Gender differences in the evaluation of coronary artery disease with a cadmium-zinc telluride camera

Alessia Gimelli · Matteo Bottai · Angela Quaranta ·
Assuero Giorgetti · Dario Genovesi · Paolo Marzullo

Received: 4 March 2013 / Accepted: 30 April 2013 / Published online: 24 May 2013
© Springer-Verlag Berlin Heidelberg 2013

Abstract

Purpose Coronary artery disease remains one of the most significant causes of morbidity and mortality among women. The published literature shows the importance of standard single photon emission computed tomography in the evaluation of women with known or suspected ischaemic heart disease, in terms of target intervention and clinical treatment. The purpose of the present study was to ascertain the diagnostic accuracy of cadmium-zinc-telluride (CZT) myocardial perfusion imaging according to gender, within a prospective database of patients with known or suspected coronary artery disease, using coronary angiography as the reference standard.

Methods Included in the study were 309 consecutive patients, of whom 248 were men (80 %), with known or suspected coronary artery disease and who had been referred to our laboratory for stress–rest myocardial perfusion imaging. All patients underwent coronary angiography within 30 days. All patients underwent a single-day stress–rest low-dose ultrafast protocol. Fifteen minutes after the end of the stress (dose range 185 to 222 MBq of ^{99m}Tc -tetrofosmin), all patients underwent the first scan with an acquisition time of 7 min. The rest scan (dose range 370 to 444

MBq of ^{99m}Tc -tetrofosmin) was acquired from 30 min to 45 min after injection, with an acquisition time of 6 min. Images were visually inspected, and summed stress scores (SSS) and summed rest scores (SRS) were obtained.

Results Image quality was graded “good” or better in more than 90 % of patients. On coronary angiography, left main trunk stenosis, left anterior descending artery stenosis, left circumflex artery stenosis and right coronary artery stenosis were seen in 3, 155, 142 and 131 patients, respectively. In women, the mean SSS and SRS were 8 ± 5 and 3 ± 1 , respectively. Semiquantitative regional and global SSS were good discriminants of coronary artery disease, and the overall area under the receiver operator characteristic (ROC) curve was 0.822 (95 % CI 0.685 – 0.959). The value was comparable to that obtained in men (overall ROC area 0.884, 95 % CI 0.836 – 0.933).

Conclusion A low-dose protocol with a CZT camera can be routinely used in women with known or suspected coronary artery disease without loss of accuracy and with lower radiation exposure of the patients.

Keywords CZT · Women · Myocardial ischaemia · Coronary artery disease

A. Gimelli (✉) · A. Quaranta · A. Giorgetti · D. Genovesi ·
P. Marzullo
Fondazione Toscana Gabriele Monasterio, CNR,
Via Moruzzi, 1, 56124 Pisa, Italy
e-mail: gimelli@ftgm.it

M. Bottai
Division of Biostatistics, Institute of Environmental Medicine,
Karolinska Institutet, Stockholm, Sweden

P. Marzullo
Institute of Clinical Physiology, CNR, Pisa, Italy

Introduction

Coronary artery disease (CAD) remains one of the most important causes of morbidity and mortality among women [1]. Although overall cardiac mortality has declined on average 3 % per year, with rates in men have decreasing substantially, little change has been reported in women [1]. As a result, interest and emphasis on research concerning women and heart disease have grown considerably, along with an increasing recognition of the importance of heart

disease in relation to the female gender. However, a worrying gap persists in knowledge, understanding and general awareness of ischaemic heart disease in women. Therefore specific diagnostic testing algorithms are necessary for early identification of at-risk women [2, 3].

Research studies in large cohorts of women undergoing single photon emission computed tomography (SPECT) myocardial perfusion imaging have shown an independent and incremental value for both diagnostic and prognostic applications [4, 5]. The possibility of identifying women at low and high risk with myocardial SPECT has been described in several reports, including >1,000 women [6–8]. Building on this result, a recent consensus paper from the American Society of Nuclear Cardiology suggested a strategy based on this technology, albeit providing little supportive clinical trial evidence [9]. In fact, published studies have demonstrated the impact of myocardial perfusion imaging by standard SPECT for the evaluation of women with known or suspected ischaemic heart disease on target intervention and clinical treatment, but they do not include current studies with the new CZT camera [10–12]. The use of a lower radiation dose while maintaining high sensitivity and specificity could not only increase patient safety but also help identify ischaemia in this complex population.

The purpose of the present study was therefore to evaluate the diagnostic accuracy of CZT myocardial perfusion imaging in relation to gender in a prospective database of patients with known or suspected CAD, using coronary angiography as the reference standard.

Material and methods

Patients

Between September 2009 and November 2012 a total of 2,673 patients, of whom 1,997 (75 %) were men, were studied with CZT imaging. From these, we enrolled a group of 309 consecutive patients (248 men, 80 %) admitted for known or suspected CAD, referred to our Institution for stress–rest SPECT and who underwent coronary angiography up to 1 month after the evaluation of ischaemia with CZT imaging. Patients with acute or recent (<3 months) ST segment elevation myocardial infarction and unstable angina were excluded from the study. The study was approved by the local ethics committee.

Stress protocols

Patients were instructed to discontinue beta-blockers, calcium antagonists and nitrates 48 h before testing. A bicycle exercise stress test (stepwise increments of 25 W every

2 min) or dipyridamole (intravenous administration of 0.56 mg/kg over 4 min) was chosen based on the patient's ability to exercise and to reach at least 85 % of the maximal age-predicted heart rate. Exercise stress testing was performed in 197 patients (64 %, 165 men) and dipyridamole stress testing was performed in 112 patients (38 %, 83 men). Of the 197 patients who underwent exercise stress testing, 148 men (90 %) and 27 women (84 %) reached 85 % of the expected maximal heart rate. Adverse events were defined according to international guidelines [13].

Acquisition protocol

Each patient underwent stress–rest CZT imaging according to a single-day protocol. The protocol for injection of ^{99m}Tc -tetrofosmin required administration of 185 – 222 MBq during stress and 370 – 444 MBq at rest. These doses were chosen as 50 % of those used previously [11, 12], as recently reported. All patients with known prior myocardial infarction were injected at rest after sublingual administration of nitrates. In all patients, CZT imaging was performed 15 min after injection of the radiopharmaceutical with an acquisition time of 7 min. According to the single-day protocol, patients were injected at rest 30 min after the end of the first acquisition and then, after an interval of 30 – 45 min, a second acquisition was carried out for 6 min. Image acquisition times were calculated so as to obtain a number of counts generally acquired by the same CZT camera after a standard tracer injection, as previously documented [11, 12].

CZT technology and acquisition protocol

The CZT camera (Discovery NM 530c; GE Healthcare, Haifa, Israel) was equipped with a multiple pinhole collimator and 19 stationary CZT detectors, simultaneously imaging 19 cardiac views. Each detector comprised 32×32 pixelated 5 mm thick (2.46×2.46 mm) elements. The system design enabled high-quality imaging of the three-dimensional volume, imaged by all detectors (quality field-of-view), where the patient's heart was to be positioned. Patients were imaged in the supine position with arms placed above the head. Once acquisition was started there was no detector or collimator motion of any kind. List-mode files were acquired and stored. Images were reconstructed on a standard workstation (Xeleris II; GE Healthcare, Haifa, Israel) using a dedicated iterative algorithm; 50 iterations were performed. A Butterworth post-processing filter (frequency 0.37, order, 7) was applied to the reconstructed slices. The tomographic studies were also reprojected into 60 planar projections to emulate a standard SPECT layout. Images were reconstructed without scatter or attenuation correction.

Image quality

The quality of both stress and rest images was graded visually on a four-point scale as 1 (poor), 2 (fair), 3 (good) or 4 (excellent). The following parameters were considered: myocardial count density and uniformity; endocardial and epicardial edge definition; visualization; and background noise, especially from the subdiaphragmatic area. Two experienced nuclear cardiologists performed the qualitative analysis independently and consensus was reached on all analyses. The readers were blinded to the coronary anatomy but not to the clinical information.

Semiquantitative analysis

Stress and rest perfusion images from the CZT camera were semiquantitatively scored according to the 17-segment model [14] of the left ventricle and a five-point scale (0 normal, 1 equivocal, 2 moderate and 3 severe reduction in radioisotope uptake, and 4 absence of detectable tracer uptake). The summed stress score (SSS) and summed rest score (SRS) were calculated by adding the scores of the 17 segments in the stress and rest images, respectively. To match the results with coronary angiograms, the 17 segments were grouped into territories of the three main coronary arteries, as previously outlined [14]: left anterior descending artery (LAD), circumflex artery (LCx) and right coronary artery (RCA). Two experienced nuclear cardiologists performed the semiquantitative analysis independently and consensus was reached on all analyses.

Analysis of gated images

Left ventricular volumes and ejection fractions were measured after stress and at baseline using previously validated software [15].

Coronary angiography

Selective conventional coronary angiography was performed using standard techniques (Innova 2000 GE; General Electric). Standard multiple projections were recorded for the left and right coronary arteries. Coronary angiograms were quantitatively analysed using an off-line computer-based software program (MEDIS CMS version 6.0; MEDIS Imaging Systems) with an automatic edge-contour detection algorithm using standard and previously validated qualitative and quantitative parameters and definitions. The variables explored were the presence of significant stenosis (≥ 70 % luminal diameter reduction) in the epicardial coronary arteries or ≥ 50 % in the left main trunk.

Statistical analysis

Continuous variables are presented as means \pm standard deviation. Where indicated, differences were assessed using Student's *t* test for paired data. Intraobserver and interobserver variability were measured using percent agreement and kappa values. Accuracy in coronary stenosis detection was assessed by the area under the receiver operating characteristic (ROC) curves. A *p* value < 0.05 was used to define statistical significance. The analyses were carried out with Stata version 11 (Statacorp, College Station, TX).

Results

Patient characteristics

Table 1 summarizes the clinical characteristics of the general population. Prior myocardial infarction was present in 50 of the 309 patients (16 %), while 71 (23 %) and 18 (6 %) had had revascularization by means of coronary angioplasty and coronary artery by-pass grafting, respectively. No adverse events were observed during stress.

Image quality and evaluation of semiquantitative scores

Stress images were graded “good” or better in 285 of 309 patients (92 %), and rest images in 278 of 309 patients (90 %). No differences were observed in image quality between men and women. In particular, in the evaluation of the stress images, the images in 228 of 248 men and in 57

Table 1 Clinical characteristics of 248 male and 61 female patients

	Men	Women
Age (years)	65 \pm 8	64 \pm 6
BMI ≥ 30 kg/m ²	119 (48 %)	30 (49 %)
Angina on effort	195 (79 %)	48 (78 %)
Dyspnoea on effort	101 (41 %)	53 (87 %)*
Mixed angina	42 (17 %)	19 (26 %)
Family history	166 (67 %)	45 (74 %)
Diabetes mellitus	135 (54 %)	12 (20 %)*
Arterial hypertension	180 (72 %)	16 (26 %)*
Hypercholesterolaemia	124 (50 %)	10 (16 %)*
Smokers	163 (65 %)	12 (20 %)*
Previous myocardial infarction	45 (18 %)	5 (8 %)*
LAD stenosis	128 (52 %)	27 (44 %)
LCX stenosis	113 (45 %)	29 (47 %)
RCA stenosis	106 (43 %)	25 (41 %)
Dipyridamole stress test	83 (33 %)	29 (47 %)*
Left bundle branch block	12 (5 %)	2 (3 %)

**p* < 0.05 , men versus women

of 61 women were graded “good” or better, and in the evaluation of the rest images, the images in 223 men and in 55 women were graded “good” or better. The intraobserver and interobserver variability were 93 % (kappa 0.86, 95 % CI 0.72 – 0.94) and 87 % (kappa 0.79, 95 % CI 0.70 – 0.92), respectively.

For the semiquantitative scores, the intraobserver and interobserver variability were 89 % (kappa 0.81, 95 % CI 0.69 – 0.92) and 84 % (kappa 0.75, 95 % CI 0.65 – 0.90), respectively.

Coronary anatomy

Left main trunk stenosis, LAD stenosis, LCx stenosis and RCA stenosis were seen in 3, 155, 142 and 131 patients, respectively. Absence of significant coronary stenosis was detected in 22/309 patients.

Correlation with coronary angiography

Women

The mean SSS and SRS were 8 ± 5 and 3 ± 1 , respectively. ROC curves in relation to global and regional SSS values are shown in Fig. 1. The overall ROC area was 0.822 (95 % CI 0.685 – 0.959), and the regional ROC areas for each vascular territory were 0.961 (95 % CI 0.914 – 1.000) for the LAD, 0.952 (95 % CI 0.896 – 1.000) for the LCx, and 0.894 (95 % CI 0.812 – 0.977) for the RCA. Using an SSS cut off of >4 , overall sensitivity and specificity were

of 88 % and 70 %, respectively, the positive and negative predictive values were 87 % and 75 %, respectively, and overall diagnostic accuracy was 83 %. In the 49 patients (80 %) without a previous history of CAD, the sensitivity and specificity were 85 % and 72 %, respectively.

Men

The mean SSS and SRS were 9 ± 5 and 2 ± 2 , respectively. ROC curves in relation to global and regional SSS values are shown in Fig. 2. The overall ROC area was 0.884 (95 % CI 0.836 – 0.933), and the regional ROC areas for each vascular territory were 0.929 (95 % CI 0.898 – 0.959) for the LAD, 0.889 (95 % CI 0.848 – 0.931) for the LCx and 0.872 (95 % CI 0.827 – 0.917) for the RCA. Using an SSS cut off of >4 , overall sensitivity and specificity were of 89 % and 78 %, respectively, the positive and negative predictive values were 87 % and 70 %, respectively, and overall diagnostic accuracy was 88 %. In the 179 patients (72 %) without a previous history of CAD, the sensitivity and specificity were 86 % and 75 %, respectively.

Gated images

In men, the mean baseline ejection fraction was 52 ± 18 %, the end-diastolic volume was 134 ± 31 ml, and the end-systolic volume was 64 ± 25 ml. Corresponding values after stress were 49 ± 21 %, 138 ± 35 ml and 68 ± 27 ml (p =not significant for all values). In women, the mean ejection fraction at rest was 52 ± 18 %, the end-diastolic volume

Fig. 1 Overall and per vessel ROC curve analysis in women. The curves represent for each SSS cut-off point pairs of sensitivity–specificity values. The areas under the ROC curves indicate very good accuracy in all vessels in the identification of CAD with the highest accuracy in the left anterior descending coronary artery territory

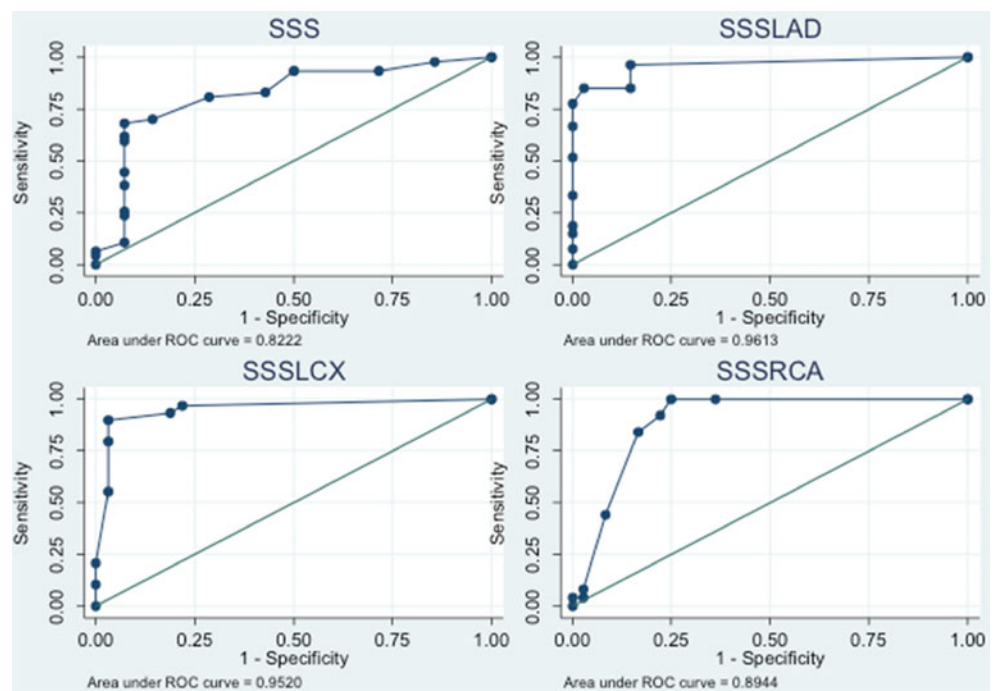
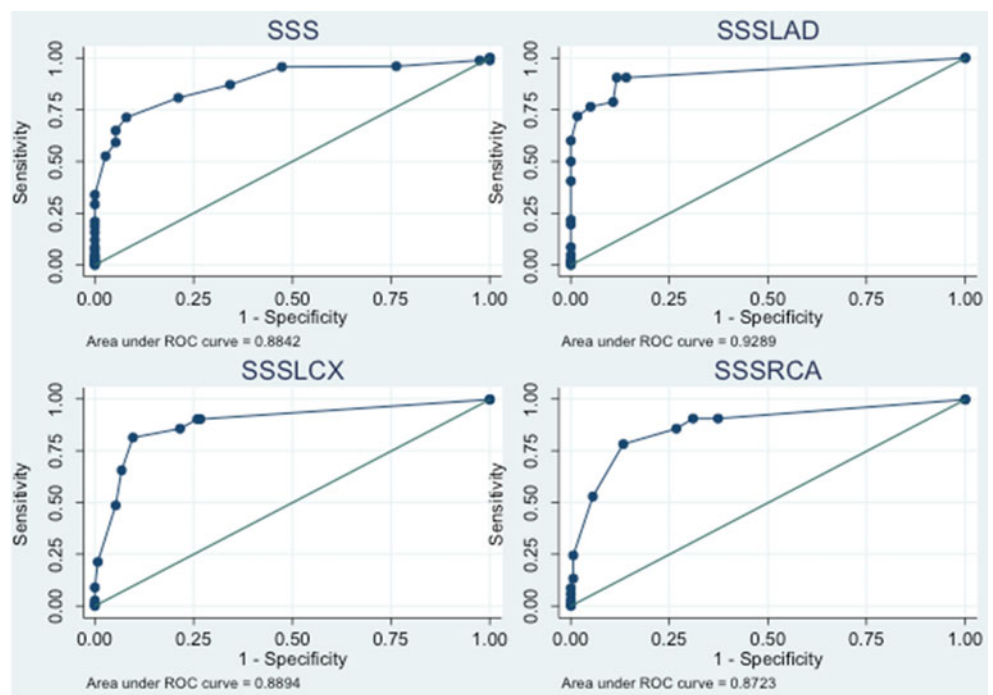


Fig. 2 Overall and per vessel ROC curve analysis in men. The curves represent for each SSS cut-off point pairs of sensitivity–specificity values. Similar to the findings in women, the areas under the ROC curves indicate very good accuracy in all vessels in the identification of CAD with the highest accuracy in the left anterior descending coronary artery territory



was 122 ± 24 ml, and the end-systolic volume was 59 ± 18 ml. Corresponding values after stress were 49 ± 19 %, 125 ± 29 ml and 61 ± 23 ml, respectively.

Discussion

In this study in a cohort of patients with known or suspected CAD no differences in sensitivity and specificity using a CZT camera were detectable between men and women. These results are comparable with those previously reported [16], and most importantly, they were obtained with a low-dose radiation protocol, an extremely important feature for the safety of patients.

The purpose of the diagnostic work-up in women with symptoms suspicious for CAD is to identify significant lesions with optimal accuracy and to lay the basis for implementing preventive and therapeutic interventions [9]. More effective diagnostic strategies are critical in women at risk of CAD, because up to 40 % of initial cardiac events are fatal [17]. As suggested in the literature, compared to men, women are initially diagnosed with more advanced CAD because of a lack of early recognition and management [18]. Therefore, a better understanding of how the accuracy variation of different noninvasive tests for CAD varies according to gender could dramatically improve the outcome in many women.

Although most early studies of the utility of myocardial perfusion imaging in establishing the diagnosis and prognosis of CAD included predominantly men, studies have established that SPECT myocardial perfusion imaging using either

^{201}Tl or $^{99\text{m}}\text{Tc}$ sestamibi/tetrofosmin provides excellent diagnostic and prognostic information in women [5, 19–20].

The data obtained in the present study, indicate that the use of a CZT camera can reproduce and improve the accuracy in detecting CAD in terms of sensitivity and specificity with a lower radiation exposure that is one of the main shortcomings of myocardial perfusion imaging by SPECT.

Previous limits overcome by CZT

Previous studies with standard myocardial SPECT in women have shown some limitations such as left ventricular size and soft-tissue attenuation that can potentially lead to reduced accuracy [21–24]. The smaller hearts in some women may potentially limit spatial resolution causing small areas of reduced perfusion to go undetected. Moreover, diagnostic specificity can also be influenced by breast tissue, which can cause false-positive results, especially in the anterior myocardial segments. These limitations have mostly been described with the use of ^{201}Tl and are theoretically decreased with higher energy $^{99\text{m}}\text{Tc}$ radioisotopes, whose use is preferable in women [19, 21]. However, the use of gating improves the specificity of SPECT in distinguishing breast attenuation from scar based on regional wall motion [25, 26]. Supplementing gated SPECT with attenuation correction may also help to further reduce artefacts related to attenuation from breast tissue.

The use of a CZT camera could overcome these limitations due to the higher spatial resolution and consequently to the better identification of myocardial walls. Increased resolution contributes to a better identification of stress defects

that may affect the myocardium in a nontransmural way. Beyond this, the real power of the CZT camera is in the design of the detector that through the multipinhole technique focuses the heart leading to a reduction in attenuation artefacts, thus increasing specificity. Finally, the increased resolution allows better evaluation of end-diastolic and end-systolic volumes with consequently better quantification of ejection fraction, without the underestimation of volumes obtained in women by standard SPECT.

Study limitations

The results of this study were based on a relatively small group of highly selected patients and this could have led to a selection bias. However, all the patients underwent coronary angiography after nuclear testing, and thus the evaluation of sensitivity and specificity was possible. Moreover, the patients showed a low occurrence of ventricular dysfunction, and thus volumes and ejection fractions were not examined in dilated hearts.

Conclusion

A low-dose protocol with a CZT camera can be routinely used in women with known or suspected CAD without loss of accuracy and with lower radiation exposure of the patients, and therefore with better safety.

Acknowledgments The authors wish to thank Mrs. Paola Migliore and Mrs. Barbara Kuhl for their help in editing the manuscript.

Conflicts of interest None.

References

- Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, 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.
- Mosca L, Banka CL, Benjamin EJ. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation*. 2007;115:1481–501.
- Holdright DR, Fox KM. Characterization and identification of women with angina pectoris. *Eur Heart J*. 1996;17:510–7.
- 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;83:660–6.
- Santana-Boado C, Candell-Riera J, Castell-Conesa J, Agudé-Bruix S, García-Burillo A, Canela T, et al. Diagnostic accuracy of technetium-99m-MIBI myocardial SPECT in women and men. *J Nucl Med*. 1998;39:751–5.
- Hachamovitch R, Berman DS, Kiat H, Bairey CN, Cohen I, Cabico A, et al. Effective risk stratification using exercise myocardial perfusion SPECT in women: gender-related differences in prognostic nuclear testing. *J Am Coll Cardiol*. 1996;28:34–44.
- Marwick T, Shaw L, Lauer M, Kesler K, Hachamovitch R, Heller G, et al. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease: Economics of Noninvasive Diagnosis (END) Study Group. *Am J Med*. 1999;106:172–8.
- Shaw LJ, Heller GV, Travin MI, Lauer M, Marwick T, Hachamovitch R, et al. Cost analysis of diagnostic testing for coronary disease in women with stable chest pain. *J Nucl Cardiol*. 1999;6:559–69.
- Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, et al. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation*. 2005;111:682–96.
- Gimelli A, Bottai M, Genovesi D, Giorgetti A, Di Martino F, Marzullo P. High diagnostic accuracy of low-dose gated-SPECT with solid-state ultrafast detectors: preliminary clinical results. *Eur J Nucl Med Mol Imaging*. 2012;39:83–90.
- Gimelli A, Bottai M, Giorgetti A, Genovesi D, Filidei E, Marzullo P. Evaluation of ischemia in obese patients: feasibility and accuracy of a low-dose protocol with a cadmium-zinc telluride camera. *Eur J Nucl Med Mol Imaging*. 2012;39:1254–61.
- Herzog BA, Buechel RR, Katz R, Brueckner M, Husmann L, Burger IA, et al. Nuclear myocardial perfusion imaging with a cadmium-zinc-telluride detector technique: optimized protocol for scan time reduction. *J Nucl Med*. 2010;51:46–51.
- Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. Guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation*. 2002;106:1883–92.
- Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–42.
- Sharir T, Berman DS, Waecter PB, Areeda J, Kavanagh PB, Gerlach J, et al. Quantitative analysis of regional motion and thickening by gated myocardial perfusion SPECT: normal heterogeneity and criteria for abnormality. *J Nucl Med*. 2001;42:1630–8.
- Iskandar A, Limone B, Parker MW, Perugini A, Kim H, Jones C, et al. Gender differences in the diagnostic accuracy of SPECT myocardial perfusion imaging: a bivariate meta-analysis. *J Nucl Cardiol*. 2013;20:53–63.
- Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics – 2010 update: a report from the American Heart Association. *Circulation*. 2010;121(7):e46–e215.
- Stangl V, Witzel V, Baumann G, Stangl K. Current diagnostic concepts to detect coronary artery disease in women. *Eur Heart J*. 2008;29(6):707–17.
- Mieres JH, Shaw LJ, Hendel RC. Consensus statement from the American Society of Nuclear Cardiology Task Force on Women and Heart Disease. The role of myocardial perfusion imaging in the clinical evaluation of coronary artery disease in women. *J Nucl Cardiol*. 2003;10:95–101.
- Friedman TD, Greene AC, Iskandrain AS. Exercise thallium-201 myocardial perfusion scintigraphy in women: correlation with coronary arteriography. *Am J Cardiol*. 1982;49:1632–7.
- Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, 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;108:1404–18.
22. Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, et al. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender optimized diagnostic strategies. *J Am Coll Cardiol*. 2006;47:S4–S20.
 23. Selvanayagam J. Women with chest pain: expanding the diagnostic armamentarium. *JACC Cardiovasc Imaging*. 2008;1:446–9.
 24. Kohli P, Gulati M. Exercise stress testing in women: going back to the basics. *Circulation*. 2010;122:2570–80.
 25. Taillefer R, DePuey EG, Udelson JE. 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.
 26. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107:2900–7.