Gender Differences in Myocardial Perfusion Defect in Asymptomatic Postmenopausal Women and Men With and Without Diabetes Mellitus

Ying-Tai Wu, PT, PhD,¹ Chen-Lin Chien, PT, PhD,^{1,2} Shan-Ying Wang, MD,^{3,4}
Wei-Shiung Yang, MD, PhD,⁵ and Yen-Wen Wu, MD, PhD³⁻⁷

Abstract

Background: To compare the results of myocardial perfusion imaging (MPI) of asymptomatic postmenopausal women and age-matched men and to investigate the effect of diabetes mellitus (DM) on gender differences and the risk estimation of coronary heart disease (CHD).

Methods: Sixty-seven postmenopausal women and 27 men low in Framingham Global Risk Score (FGRS) were recruited from year 2008 to 2009 in northern Taiwan. Each subject underwent blood tests, a cardiopulmonary exercise test, an electrocardiograph (ECG), and MPI.

Results: Women had similar percentages of predicted oxygen consumption and ECG changes at peak exercise, but lower oxygen pulse and rate-pressure product. They also had significantly higher summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) than men, despite showing much lower scores for the FGRS than men. Women with DM had a lower 10-year risk of CHD assessed by the United Kingdom Prospective Diabetes Study (UKPDS) risk engine, but significantly higher SSS and SDS than men. In the subjects with abnormal MPI, the extent of ischemia was small to moderate in men, whereas in 50% of the women, the extent of ischemia was large.

Conclusion: The results of this preliminary study suggest that asymptomatic postmenopausal women had more abnormalities in MPI and those with DM had a higher SSS and SDS than age-matched men. The risk of CAD may still be underestimated by the UKPDS.

Introduction

MENOPAUSE IS A RISK FACTOR for coronary heart disease (CHD) in women.^{1,2} Risk stratification helps optimize the management for postmenopausal women. Besides the conventional Framingham Global Risk Score (FGRS), a new guideline for classification of cardiovascular disease risk in women has been developed.³ Women with either diabetes mellitus (DM) or chronic kidney disease are at high risk. Increasing evidence has indicated the diagnosis of DM to be a risk factor for both men and women. The United Kingdom Prospective Diabetes Study (UKPDS) risk engine has been used to estimate the risk of CHD and stroke, especially in people with DM.⁴

Exercise myocardial perfusion imaging (MPI) by thallium-201 single photon emission computed tomography (SPECT) is a noninvasive screening tool for people at risk of CHD. Cardiac death risk has been reported to increase significantly in both men and women as a function of MPI results.⁵ However, the timing of assessment or the absolute indication remains disputed. It has been clinically useful to classify most elderly subjects (≥ 75 years old) into low- and high-risk categories, which has allowed for the accurate prediction of outcomes in both genders.⁶ Lee et al.⁷ reported myocardial perfusion defects in nearly one fifth of asymptomatic elderly women, and the rate was much higher in those with CHD risks. Little about gender differences in MPI has been reported in asymptomatic older women after

¹School and Graduate Institute of Physical Therapy, College of Medicine, National Taiwan University, Taipei, Taiwan.

²Department of Respiratory Therapy, College of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan.

³Department of Nuclear Medicine, National Taiwan University Hospital, Taipei, Taiwan.

⁴Department of Nuclear Medicine, Far Eastern Memorial Hospital, Taipei, Taiwan.

⁵Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.

⁶Cardiology Division of Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City, Taiwan.

⁷National Yang-Ming University College of Medicine, Taipei, Taiwan.

menopause. Moreover, the added effect of DM on MPI in this age population has rarely been reported.

The purposes of this study were to study the prevalence of abnormal MPI in asymptomatic postmenopausal women in comparison with age-matched men, and to investigate the impact of DM on MPI in both genders.

Materials and Methods

Study design and population

This prospective study included 67 postmenopausal sedentary women (58.8 ± 5.9 years old) and 27 age-matched men (58.2 ± 5.6 years old) who responded to the advertisement posted in the hospital and nearby communities from year 2008 to 2009 in northern Taiwan. They were all asymptomatic and free of cardiac diseases or events, and about 50% of them had DM. Subjects were excluded if they had any one of the following conditions: impaired renal function (serum creatinine level ≥ 1.5 mg/dL), impaired liver function (total bilirubin level ≥ 2 mg/dL, alanine aminotransferase $\geq$ twice the upper limit of the normal range), abnormal resting electrocardiographic results (such as ST-segment depression ≥ 1 mm, deep negative T waves, left bundle branch block, pathologic Q waves, or arrhythmias), active pulmonary disease, weight loss > 10 kg in the past 6 months, any ongoing or unstable medical conditions, or if the women were taking hormone replacement therapy.

All of the participants underwent a physical examination and a resting electrocardiogram (ECG). Medical history and clinical and demographic data were collected. All subjects underwent blood tests, a cardiopulmonary exercise test (CPET), and an ECG-gated Treadmill ^{201}Tl SPECT MPI. This study was reviewed and approved by the institutional ethics committee. Written informed consent was obtained after explaining the study design and procedures prior to the study.

Laboratory tests

Peripheral venous blood samples were taken after fasting more than 8 hours. Measurements of glucose, hemoglobin A1c (HbA1c), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride, and C-reactive protein (CRP) were performed in the central laboratory of the hospital.

Estimate of 10-year risks of coronary events and stroke

We used two methods to evaluate the risks of CHD and stroke: the FGRS and the UKPDS risk engine. The global 10-year risk of developing a hard coronary heart disease outcome (myocardial infarction or coronary death) was estimated using the FGRS according to the third report of the National Cholesterol Education Program Adult Treatment Panel.⁸ The cardiovascular risk was calculated based on the traditional cardiovascular risk factors, including age, total cholesterol, HDL-C, systolic blood pressure (BP), treatment for hypertension, and cigarette smoking; risk was then classified as high ($> 20\%$), intermediate ($10\% - 20\%$), or optimal ($< 10\%$) risk.⁸ The UKPDS risk engine was published in 2001 for inclusion of diabetes-specific variables, such as duration and HbA1C in predicting rates of CHD and stroke in patients with DM.^{4,9}

Cardiopulmonary exercise test

Each participant underwent a maximum CPET on a treadmill using the Bruce protocol with continuous ECG monitoring after the resting heart rate (HR) and blood pressure were measured. When the peak level of exercise was reached, respiratory frequency (RR), minute ventilation ($\dot{V}_E$), O_2 consumption ($\dot{V}\text{O}_2$), and CO_2 production ($\dot{V}\text{CO}_2$) were measured breath-by-breath and averaged over a 30-second interval with a Vmax Series V229 gas analyzer (Vmax229, Sensor Medics, Anaheim, California, CA). The termination criteria included volitional exhaustion, signs of exercise intolerance, $\text{HR} \geq 90\%$ of the age-predicted maximum ($220 - \text{age}$), respiratory exchange ratio ≥ 1.15 , or abnormal ECG. Heart rate recovery 1 (HRR1) and heart rate recovery 2 (HRR2) were defined as the decrease in HR between peak exercise and 1 minute into the recovery period or 2 minutes into the recovery period, respectively, with no cool-down period.

ECG-gated treadmill ^{201}Tl SPECT

Treadmill SPECT testing using ^{201}Tl as a radiotracer was performed in accordance with guidelines from the American Society of Nuclear Cardiology and the American Heart Association^{10,11} within a week after the CPET. The Bruce exercise protocol with continuous 12-lead ECG monitoring was used. At near maximal stress, a 3 mCi dose of ^{201}Tl was injected intravenously, and exercise was continued for another 1 minute. Poststress images were acquired within 5 minutes after ^{201}Tl injection.

The images were acquired on a dual-head SPECT/CT scanner (Symbia T2, Siemens, Medical Solution Inc., Hoffman Estates, IL) equipped with low-energy general purpose collimators. A noncircular 180° acquisition for 64 projections at 20 seconds (poststress) and 25 seconds (at redistribution) per projection were used. We set two energy windows at 72 keV ($\pm 10\%$) and at 167 keV ($\pm 10\%$) for ^{201}Tl . All projection images were transferred in DICOM format and processed using syngo MI applications (Siemens). Data were stored in a 128×128 matrix with a zoom factor of 1.0. Nongated myocardial perfusion images were reconstructed using a Flash 3D method with a Gaussian filter (eight iterations, eight subsets; FWHM 8.4 mm), and resampling the data along the short, vertical long, and horizontal long axes for display. Breath-hold CT was performed after the poststress emission acquisition. Emission data were reconstructed iteratively with CT-derived attenuation correction using ordered-subsets expectation maximization. The non- and attenuation-corrected images, along with accompanying ECG-gated SPECT images were presented for blinded consensus interpretation.

SPECT analysis

After reconstruction of the gated short-axis slices, QPS software and QGS software (Cedar Sinai Medical Center, Los Angeles, CA) were used for visual interpretation and subsequent quantitative analysis.¹² The diagnostic performance of this quantitation software was confirmed.¹³ The myocardium was divided into a 20-segment model, and each segment was scored using a standard 5-point scoring system (0 = normal uptake of the radioactive isotope, 1 = slight reduction of uptake, 2 = moderate reduction of uptake, 3 = severe reduction of

uptake, and 4=absence of uptake). The segmental perfusion scores during stress and at rest were added to create the summed stress scores (SSS) and the summed rest scores (SRS), respectively. The summed difference score (SDS) was the difference between SSS and SRS, indicating the extent of ischemia. The extent of ischemia was expressed as % ischemic myocardium (% ischemic myocardium = $[\text{SDS}/80] \times 100$) and abnormal MPI was defined as the extent of ischemia $\geq 2.5\%$, with 2.5%–7.4% indicating a small to moderate extent and $\geq 7.5\%$ indicating a large extent of ischemia.¹⁴ We also calculated the left ventricular ejection fraction (LVEF) at rest with the aid of quantitative programs and assessed the nonperfusion abnormality of ischemic ECG changes.^{15,16} Two experienced readers, who were blinded to the patients' clinical information and results of CPET, participated in this study, with excellent intra- and interreader reproducibility for QGS and QPS analyses ($r \geq 0.99$).¹⁷

Data analysis and statistics

All statistical analyses were performed using SPSS 13.0 for Windows (SPSS Inc., Chicago IL). All data were presented as mean $\pm$ SD for continuous variables and numbers (percentage) for categorical variables. Continuous variables were compared between groups by *t*-test. Categorical variables were compared between groups by chi-square or Fisher's exact test. A subgroup analysis on subjects with DM ($n=44$) was also performed using the same statistics to test the gender differences. A *p* value < 0.05 was considered statistically significant.

Results

Men had higher body height, body weight, waist circumference, and percentage that smoked. Higher levels of total cholesterol and HDL-C, but similar levels of LDL-C and triglycerides in women than men were noted. There were no other between-group differences (Table 1).

Men had higher HR, BP, and rate-pressure product (RPP) at rest and during peak exercise (Table 2), but there were no gender differences in the change or reserve of RPP. The absolute peak exercise capacity of men was higher than women, with a similar percentage of the predicted maximum between genders. Slightly more women developed ST depression (≥ 1 mm) and arrhythmia, with no statistical significance (Table 3). The QPS and QGS analyses determined LVEF values were significantly higher in women. All of the treadmill ECG and SPECT data were of adequate quality for interpretation. Women had significantly higher myocardial perfusion scores (SSS, SRS, and SDS) than men, indicating mildly abnormal values. However, 10-year risks of developing hard coronary heart disease calculated by FGRS was significantly higher in men than in women ($10.7 \pm 5.3\%$ vs. $2.3 \pm 1.7\%$, $p=0.001$).

Among subjects with DM, men had significantly higher 10-year risks of nonfatal or fatal CHD than women. However, women had higher SSS and SDS than men and half of the subjects with abnormal MPI had a large extent of ischemic myocardium in contrast to a small to moderate extent in men (Table 4).

Discussion

The women and men subjects had comparable exercise capacity based on the predicted percentage of peak VO_2 . The

TABLE 1. BASELINE CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS^a

	Female (n = 67)	Male (n = 27)	p value
Age, years	58.8 $\pm$ 5.9	58.1 $\pm$ 5.6	0.621
Body height, cm	156.3 $\pm$ 4.8*	167.8 $\pm$ 5.6	0.001*
Body weight, kg	60.1 $\pm$ 9.3*	70.7 $\pm$ 8.5	0.001*
Body mass index, kg/m ²	24.6 $\pm$ 3.5	25.1 $\pm$ 2.6	0.473
Waist circumference, cm	80.5 $\pm$ 9.2*	89.5 $\pm$ 6.9	0.001*
Current smoker	0 (0%)	7 (26%)	0.001*
Hypertension, n (%)	39 (58)	12 (44)	0.249
Dyslipidemia, n (%)	25 (37)	8 (32)	0.249
Diabetes mellitus, n (%)	29 (43)	15 (56)	0.403
Fasting glucose, mg/dL	113.8 $\pm$ 32.6	113.1 $\pm$ 28.2	0.920
HbA1c, %	6.6 $\pm$ 1.2	6.4 $\pm$ 0.9	0.457
Total cholesterol, mg/dL	200.0 $\pm$ 34.6	177.7 $\pm$ 34.9	0.006*
HDL-C, mg/dL	54.0 $\pm$ 11.4	45.8 $\pm$ 8.3	0.001*
LDL-C, mg/dL	108.0 $\pm$ 30.1	97.5 $\pm$ 32.9	0.142
Triglyceride, mg/dL	133.6 $\pm$ 107.6	133.0 $\pm$ 108.9	0.982
C-reactive protein, mg/dL	0.24 $\pm$ 0.35	0.24 $\pm$ 0.71	0.990
Framingham Global Risk Score, %	2.3 $\pm$ 1.7	10.7 $\pm$ 5.3	0.001*

^aData are presented as mean $\pm$ SD or as numbers with percentage of total in parentheses.

* $p < 0.05$

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

asymptomatic postmenopausal women, with lower conventional cardiovascular risks than men, had higher SSS and SDS. More female subjects with abnormal myocardial perfusion had a larger extent of ischemia than men. Similarly, with respect to diabetes, women had lower risk of CHD according to the UKPDS, but had significantly higher SSS and SDS than men.

Clinical investigators have tried to predict cardiac events using variables derived from CPET. The RPP or so-called double product, indicative of myocardial oxygen consumption, has been reported to have prognostic value for predicting cardiovascular mortality.^{18,19} Our study indicated that the values of RPP at rest and during peak exercise were higher in men than in women; however, the change in RPP with exercise was not different between genders if they had similar exercise capacities. Reduced HRR has been used as a marker of adverse cardiovascular prognosis.²⁰ A high prevalence of abnormal stress MPI and high risk of stress MPI was reported if $\text{HRR} \leq 12$ beats.²¹ The present subjects had normal HRR1 in both genders. In this study, RPP, UKPDS, FGRS, and HRR1 all showed that the men and women were at a low risk of future cardiac events.

Subjects with normal stress MPI have been reported to have a low risk of cardiac events, while those with abnormal stress MPI may need strict control of the underlying disease or CHD risk.^{22,23} The women subjects in the present study were at a

TABLE 2. CARDIOPULMONARY EXERCISE PERFORMANCE RESULTS AT REST AND DURING EXERCISE^a

	Female (n=67)	Male (n=27)	p value
At rest			
HR, bpm	72.8±9.2	77.7±10.1	0.024*
Blood pressure			
Systolic, mm Hg	125.4±15.3	135.0±12.2	0.004*
Diastolic, mm Hg	78.0±9.6	82.3±7.5	0.041*
RPP, beat/min×mm Hg	9128.5±1571.0	10464.7±1428.8	<0.001
Peak exercise			
HR, bpm	140.1±14.1	145.2±7.7	0.029*
Blood pressure			
Systolic, mm Hg	178.7±21.3	192.1±18.8	0.005*
Diastolic, mm Hg	86.6±12.3	82.0±9.7	0.082
RPP, beat/min×mm Hg	25085.3±4104.8	27894.1±3207.1	0.002*
RPP change with exercise, beat/min×mm Hg	15956.8±3658.4	17429.4±3456.2	0.076
VO ₂₂ , mL/kg/min	20.2±3.7	22.4±2.7	0.005*
% of predicted peak VO ₂₂	76.5±13.1	80.3±13.1	0.207
O ₂ pulse, mL/beat	8.7±1.7	10.9±1.3	0.001*
Ventilation, L/min	43.3±10.1	53.4±7.7	0.001*
Tidal volume, L	1.2±0.2	1.6±0.3	0.001*
Exercise duration, min	5.2±1.2	6.0±1.1	0.004*
HRR1, bpm	29.1±9.5	28.9±9.4	0.912
HRR2, bpm	46.0±11.3	44.1±9.9	0.456

^aData are presented as mean±SD.

**p*<0.05.

RPP, rate-pressure product; HR, heart rate; HRR1 and HRR2, heart rate recovery 1 and 2, which are defined as the decrease in heart rate between peak exercise and 1 or 2 minutes into the recovery period; VO₂, O₂ consumption.

low risk of CHD as estimated by FGRS, but had higher SSS and SDS than men. Additionally, the abnormal MPI in women was associated with a large extent of ischemia with significant gender differences. Our study pointed out the discrepant results using different tools, and screening by FGRS may not be appropriate for postmenopausal women. More studies concerning the early detection of CHD in postmenopausal women are needed.

DM is believed to be a risk factor for the development of CHD and an independent predictor of silent ischemia.¹⁴ Zellweger et al.¹⁴ reported a 0.5% annual hard event (cardiac death or nonfatal myocardial infarction) rate after 1.9±0.7 years, while those with 7.5% of ischemic myocardium had an annual rate of 3.2%. We found that the 10-year risk of CHD (myocardial infarction or cardiac death) was significantly higher in men than in women using the FGRS or UKPDS risk engine for evaluation. The SSS and SDS were significantly higher in diabetic women, but not the SRS, which may be partly attributed to the limited number of subjects. It reinforced the importance of exercise challenge to detect the abnormality in MPI for women with DM. These women also tended to have a large extent of ischemic myocardium on MPI (*p*=0.054). The gender differences in older adults with diabetes need to be elucidated and studies of a large sample size are indicated. Previous studies also suggested that diabetic women have a poorer cardiovascular prognosis than diabetic men.⁵

The physiological mechanisms for the high prevalence of abnormal MPI in diabetic women compared with diabetic men are not clear. The association might be related to the greater abnormalities in lipid profile or insulin resistance, which in turn may accelerate vascular disease.²⁴ However, the subjects with diabetes in the present study were in good glycemic control with similar levels of LDL-C, HDL-C, and triglycerides

between genders (Table 4). The cardiovascular risk of diabetic women should be addressed further in a large population.

There were some intrinsic physiological differences between genders, which resulted in gender-specific reference limits in the functional parameters of SPECT MPI.^{17,25–27}

TABLE 3. RESULTS OF ELECTROCARDIOGRAM-GATED SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY BY GENDER^a

	Female (n=67)	Male (n=27)	p value
Summed stress score	5.1±4.7	2.6±2.6	0.010 ^{b,*}
Summed rest score	1.5±2.3	0.5±1.2	0.034 ^{b,*}
Summed difference score	3.5±3.2	2.1±1.9	0.040 ^{b,*}
Abnormal MPI, <i>n</i> (%)			0.016*
2.5%–7.4% ischemic myocardium	15 (22)	10 (37)	
≥7.5% ischemic myocardium	11 (16)	0	
Abnormal ECG during exercise, <i>n</i> (%)			
ST depression ≥1 mm	10 (15)	0 (0)	0.105
Significant arrhythmia	3 (4)	2 (7)	0.240
Significant ischemia, <i>n</i> (%)	10 (15)	2 (7)	0.264
Resting LV ejection fraction, %	80.0±10.5 ^c	61.9±7.8	0.001*

^aData are presented as mean±SD or as numbers with percentage in parentheses. Continuous variables were compared between groups by *t*-test. Categorical variables were analysis by the Fisher's exact test.

^bCategorical variables were analysis by the non-parametric test.

^c*n*=65, two subjects did not undergo the ECG-gated SPECT.

**p*<0.05.

MPI, myocardial perfusion image; ECG, electrocardiogram; LV, left ventricle.

TABLE 4. SUBGROUP ANALYSIS ON SUBJECTS WITH DIABETES MELLITUS^a

	Female (n = 29)	Male (n = 15)	p value
Age, years	59.2 ± 6.2	57.5 ± 4.2	0.332
Duration of being diagnosed as diabetes, years	6.7 ± 6.4	10.1 ± 6.8	0.137
10-year risk of CHD and stroke ^b			
Nonfatal CHD	9.8 ± 4.5	17.0 ± 6.5	<0.001*
Fatal CHD	6.3 ± 4.0	10.7 ± 4.9	0.003*
Nonfatal stroke	5.3 ± 3.6	7.6 ± 3.2	0.050
Fatal stroke	0.7 ± 0.6	1.1 ± 0.5	0.064
Lipid profile			
Total cholesterol, mg/dL	189.0 ± 34.1	161.5 ± 29.4	0.013*
HDL-C, mg/dL	50.9 ± 9.6	45.1 ± 8.8	0.061
LDL-C, mg/dL	101.2 ± 27.7	90.5 ± 26.2	0.226
Triglyceride, mg/dL	136.7 ± 83.8	105.5 ± 68.2	0.221
SPECT analysis			
Summed stress score	5.5 ± 4.1	2.5 ± 2.0	0.015 ^{c,*}
Summed rest score	1.8 ± 2.4	0.5 ± 0.8	0.093 ^c
Summed difference score	3.7 ± 2.8	2.0 ± 1.7	0.033 ^{c,*}
Abnormal MPI, n (%)			0.054
2.5%–7.4% ischemic myocardium	6 (21)	6 (40)	
≥7.5% ischemic myocardium	6 (21)	0	

^aData are presented as mean ± SD or as numbers with percentage in parentheses. Categorical variables were analyzed by the Fisher's exact test.

^bRisks were assessed by United Kingdom Prospective Diabetes Study risk engine.

^cCategorical variables were analyzed by the nonparametric test.

**p* < 0.05.

CHD, coronary heart disease.

Studies for LV functional parameters determined by gated SPECT showed a higher ejection fraction (EF) and lower end-systolic volume (ESV) and end-diastolic volume (EDV) in women; partially due to limited resolution leading to underestimation of ESV and subsequent overestimation of EF in those with small hearts.¹⁷ It has been reported that treadmill SPECT MPI provides higher negative predicted values for primary and secondary cardiac events than treadmill exercise ECG based on a meta-analysis published in 2007, and it has been useful in both men and women.²³ However, additional studies on the timing of using this diagnostic tool to identify an increased risk of CHD for postmenopausal women with or without diabetes are definitely needed because relatively few women have been involved in diagnostic studies in the past.^{28,29}

There were several limitations of this study. First, women tend to have more breast attenuation in the anterior wall in SPECT²⁶; however, the breast attenuation problem may be less in Asian populations.^{30,31} Second, no coronary angiography was performed in the present study. It is difficult to obtain informed consent for asymptomatic persons to undergo angiography. Third, the present study lacks a long-term follow-up to compare with the survival and cardiac events and further evaluate the prognostic evidence.

Conclusion

The preliminary study suggests that postmenopausal women with or without DM had a tendency to present abnormal SPECT myocardial perfusion despite an asymptomatic status and low risk of CHD as determined by FGRS and UKPDS. Normal rate-pressure product reserve, HR reserve, and LVEF may not be sufficient to guarantee normal myocardial perfusion in asymptomatic postmenopausal women.

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Disclosure Statement

No competing financial interests exist.

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Address correspondence to:

Yen-Wen Wu, MD, PhD

Cardiology Division of Cardiovascular Medical Center

and Department of Nuclear Medicine

Far Eastern Memorial Hospital

No. 21, Sec. 2, Nanya S. Rd., Banciao Dist.

New Taipei City, 220

Taiwan

E-mail: wuyw0502@gmail.com