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Gender Differences in Myocardial Blood Flow Dynamics

Lipid Profile and Hemodynamic Effects

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OBJECTIVES The purpose of the study was to compare myocardial blood flow (MBF) in hyperlipidemic postmenopausal women and age-matched hyperlipidemic men, and to analyze the relationship between cholesterol subfractions and myocardial blood flow in men and women.

BACKGROUND Women are protected from coronary artery disease (CAD) events until well after menopause, in part due to gender-specific differences in lipid profiles.

METHODS To examine the effect of these influences on coronary microcirculation, MBF was quantitated with N-13 ammonia/PET (positron emission tomography) at rest and during adenosine hyperemia in 15 women and 15 men, all nondiabetic, who were matched for age and total cholesterol levels (53 ± 4 vs. 50 ± 8 years, p = NS, 6.44 ± 1.1 vs. 6.31 ± 0.85 mmol/liter, or 249 ± 41 vs. 244 ± 33 mg/dl, p = NS).

RESULTS Women had significantly higher high density lipoprotein (HDL) and lower triglyceride (Tg) levels than did men, and they showed significantly higher resting MBF and stress MBF levels. Significant correlations were found between resting and hyperemic MBF and HDL and Tg levels ($r = 0.44$, $p < 0.02$ for stress MBF vs. HDL; $r = 0.48$, $p < 0.007$ for stress MBF vs. Tg). Gender was the strongest predictor of hyperemic MBF in multivariate analysis. Women responded to adenosine hyperemia with a significantly higher heart rate than did men, and hemodynamic factors correlated significantly with blood flow both at rest and during stress.

CONCLUSIONS These data suggest that the favorable lipid profile seen in women may be associated with preserved maximal blood flow in the myocardium. (J Am Coll Cardiol 1999;33:463–70) © 1999 by the American College of Cardiology

Elevated serum cholesterol is a well-established risk factor for the subsequent development of coronary heart disease. Recent studies have established that cholesterol-lowering therapy can result in a decreased incidence of myocardial infarctions, and an overall decrease in cardiovascular mortality both in the primary and secondary prevention of coronary heart disease (1,2). Part of this benefit appears to result from stabilization of the coronary vascular endothelium, while relatively little regression of atherosclerotic plaque can be demonstrated (3). Several investigators have demonstrated attenuated hyperemic myocardial blood flow and coronary flow reserve, an integrating parameter of endothelial function and vascular smooth muscle relaxation, in male subjects with elevated cholesterol levels prior to the angiographic appearance of coronary artery disease (4,5). Although myocardial blood flow and flow reserve have been studied in both men and women with respect to changes observed during aging, no studies to date have systematically examined myocardial blood flow and flow reserve in women with risk factors for coronary artery disease (CAD) (6). Women are known to be protected from CAD events until after menopause, when the risk of myocardial infarction increases sharply and begins to parallel the risk for men (7). Part of this protective effect is felt to be due to higher levels of high density lipoproteins (HDLs) and lower levels of low density lipoproteins (LDLs), triglycerides (Tgs), and total cholesterol in premenopausal women (8). The purpose of this study, therefore, was to compare myocardial blood flow in hyperlipidemic postmenopausal women with that of age-matched hyperlipidemic men, and to analyze the relationship between cholesterol subfractions and myocardial blood flow in men and women.

METHODS

Study design and criteria. Fifteen postmenopausal women with elevated total cholesterol levels and one or more

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Abbreviations and Acronyms

CAD = coronary artery disease
HDL = high density lipoprotein
HR = heart rate
LAD = left anterior descending
LCx = left circumflex
LDL = low density lipoprotein
MBF = myocardial blood flow
MBP = mean blood pressure
MI = myocardial infarction
PET = positron emission tomography
PRP = pressure rate product
RCA = right coronary artery
SPECT = single photon emission computed tomography
Tg = triglyceride

additional risk factors for CAD were recruited for the study, as were 15 asymptomatic men with hyperlipidemia and one or more additional risk factors. Patient characteristics are shown in Table 1. All men had undergone stress perfusion imaging within 90 days of the PET (positron emission tomography) study, and had normal studies. Three of the women had symptoms of nonexertional chest pain; these three patients had undergone cardiac catheterization and had been shown to have normal coronary arteries. The remaining 12 women were asymptomatic; in these patients, normal semiquantitative PET studies were considered sufficient to rule out epicardial coronary disease. Exclusion criteria for all persons included diabetes mellitus and electrocardiogram (ECG) evidence of myocardial infarction or left ventricular hypertrophy.

All participants were fasting for at least 8 h, and caffeine intake was stopped 24 h prior to the PET study. One patient was on a long-acting theophylline preparation; this was held for 72 h prior to the PET study. Blood samples for determination of the lipoprotein status were obtained after overnight fast just before the PET scan.

Table 1. Patient Characteristics

Parameter	Women (n = 15)	Men (n = 15)	p
Age (years)	53 ± 4	50 ± 8	0.19
TChol (mg/dl)*	249 ± 41	244 ± 33	0.71
LDL (mg/dl)*	162 ± 52	170 ± 32	0.58
HDL (mg/dl)*	72 ± 19	39 ± 9	< 0.001
Tg (mg/dl)*	114 ± 63	181 ± 59	0.01
TChol/HDL ratio	3.7 ± 1.3	6.6 ± 1.6	< 0.001
LDL/HDL ratio	2.5 ± 1.2	4.6 ± 1.1	0.0001
Smoking Hx	6	3	0.25
Htn	4	3	0.68
Family Hx	7	15	< 0.01

* To convert values to millimoles per liter, multiply by 0.02586.
TChol indicates total cholesterol; HDL, high density lipoprotein fraction; LDL, low density lipoprotein fraction; Tg, triglycerides; Hx, history; Htn, hypertension (systolic blood pressure >150, diastolic blood pressure >95, or current treatment for hypertension). Values are given as mean ± SD for continuous variables.

The study protocol was approved by the institutional review boards of both the University of Michigan and the Technical University of Munich. Each patient gave informed consent prior to being enrolled into the study.

PET imaging protocol. N-13 ammonia was synthesized by the $^{16}O(p,a)^{13}N$ reaction as described by Gelbard et al. (9). Dynamic PET measurements were performed using a whole-body PET-scanner (Siemens/ECAT 931, 951R/31, Exact 47, or CTI 931), which allows simultaneous acquisition of 15 contiguous transaxial images. After placement in the PET scanner, a "scout scan" was obtained to align the heart within the field of view of the scanner using 74 MBq N-13 ammonia. The patient's position with respect to the camera was checked by a cross-shaped, low-power laser beam and pen markers on the patient's skin. A 15-min transmission scan was then acquired to correct for photon attenuation using retractable germanium-68 ring sources. After completion of the transmission scan, 740 MBq N-13 ammonia diluted in 10 cc of normal saline was administered as a slow bolus over 30 s using a volumetric pump (Harvard model 975, Harvard Apparatus, South Natick, MA) via a peripheral intravenous (IV) line. At study onset, dynamic scan acquisition was initiated with varying frame duration (12 × 10 s/4 × 15 s/4 × 30 s/3 × 300 s). The total scanning time was 20 min.

After acquisition of the baseline N-13 ammonia study, at least 50 min was allowed for N-13 decay (physical half-life 9.9 min). During this time, residual N-13 activity from the preceding scan had physically decayed to <3% of its initial activity.

For the stress study, myocardial blood flow was increased by IV adenosine infused at 0.14 mg/kg/min over 5 min using a Harvard pump. Heart rate and blood pressure were monitored at 1-min intervals during the first 10 min of the study, and at the conclusion of scanning. Mean blood pressure (MBP) was calculated as (systolic blood pressure +2 × diastolic blood pressure)/3. Pressure-rate product (PRP) was calculated as heart rate multiplied by systolic blood pressure. The ECG was continuously monitored. Three minutes after the onset of the adenosine infusion, N-13 ammonia was injected. The PET data acquisition protocol was identical to the baseline study.

Image processing. Images were reconstructed using a Hann filter with a cutoff frequency of 0.35. Slice thickness for the 15 contiguous transaxial images was 6.75 mm, resulting in an image resolution of 8.5 ± 0.35 mm at full-width at half maximum (FWHM) in-plane and 6.6 ± 0.49 mm FWHM in the axial direction. The PET data analysis was performed by one experienced observer who evaluated all baseline rest/stress studies. Using a SUN workstation (SUN Microsystems), 12 transaxial images were created in the short-axis view of the heart. The vertical and horizontal cardiac long-axis angles were defined using the last frame of the N-13 ammonia dynamic sequence with

Table 2. Hemodynamic Findings

Parameter	Women (n = 15)		Men (n = 15)	
	Rest	Adenosine	Rest	Adenosine
Heart rate (bpm)	71 ± 8	102 ± 16*	69 ± 11	79 ± 41*
Systolic BP (mm Hg)	125 ± 20	129 ± 25	133 ± 15	131 ± 15
Diastolic BP (mm Hg)	80 ± 15	80 ± 14	80 ± 11	76 ± 9
Pressure Rate Product	8835 ± 1708	13160 ± 3257*	9180 ± 2076	10401 ± 2338†§
Mean BP (mm Hg)	95 ± 15	96 ± 16	98 ± 11	95 ± 10

* $p < 0.05$ vs. resting value. † p = NS vs. resting value. § $p < 0.02$ vs. women.
BP = blood pressure.

the best tissue-to-blood ratio, and were subsequently used for the reorientation of all 21 frames.

Quantification of myocardial blood flow. A previously described method for automated region definition was used for kinetic analysis of the acquired dynamic data set. Based on radial activity profiles, the algorithm automatically defines myocardial regions containing a blood volume fraction of 50% to 60%. The algorithm incorporates corrections for partial volume effects and blood-to-tissue cross-contamination into the model equation (10).

Using the described algorithm, 12 myocardial regions per plane were defined in 5 to 8 planes of the last time-frame featuring a high contrast between blood and tissue. These regions were subsequently copied to all remaining time-frames of the dynamic sequence. Before time-activity curves were generated, the dynamic image sequence was corrected for patient motion as described previously (11). The dynamic image set was sampled, and time-activity curves were generated in 12 myocardial sectors for each plane of the left ventricle.

To assess the left ventricular blood pool time-activity curve, a small circular region (diameter 3 pixels, approximately 9 mm) was drawn in two or three of the most basal planes of the resliced image set and copied to the entire serially acquired image sequence to obtain the arterial input function (10). The time-activity curves were then fitted with a previously validated three-compartment tracer kinetic model (12).

In addition to calculating the myocardial blood flow (MBF) for the left ventricle as a whole, MBF was determined for each of three vascular beds (left anterior descending [LAD], left circumflex [LCx], and right coronary artery [RCA]). All PET studies were also analyzed semiquantitatively by comparison with a normal database, as previously described (13).

Statistical analysis. Mean value and standard deviation were calculated for each continuous variable. A two-tailed Student *t* test for unpaired data sets was used to analyze for statistical significance, with a p value less than 0.05 considered significant. McNemar's test was used to analyze differences between groups for categorical variables. Univariate and multivariate stepwise linear regression analyses were performed as described below to analyze the effects of each variable on resting and stress blood flow. Univariate regression analysis was performed using Statview 4.1 for the Macintosh (Abacus Concepts) with each risk factor separately selected as the independent variable, analyzed against MBF selected as the dependent variable. This analysis provides an R value as well as a p value for significance, and allows for the creation of a scattergram for graphic display of results. Multivariate analysis was performed using Systat 5.2.1 for the Macintosh (Systat) to perform backward stepwise regression analysis using the multivariate general linear hypothesis function, with minimum tolerance for entry into the model set at 0.01, and p value to enter as well as to remove variables set at 0.15.

RESULTS

A total of 30 patients (15 men and 15 women) underwent dynamic N-13 ammonia PET at rest and during adenosine-induced hyperemia. The subjects were matched for age and total cholesterol levels.

Baseline patient characteristics. Age, lipid profile values, and presence of other risk factors for CAD are shown for each group in Table 1. Significantly more men than women had a family history of CAD, defined as myocardial infarction (MI) or revascularization before age 60 in a first-degree relative; other risk factors were equivalent between the two groups. Although the men and women had equivalent total cholesterol and LDL levels, the women had significantly higher HDL levels, and lower triglyceride (Tg) levels. In addition, the total cholesterol/HDL and LDL/HDL ratios were significantly lower for the women than for the men, indicating more favorable lipid profiles for the women.

Hemodynamic findings. Table 2 summarizes the hemodynamic characteristics at rest and during adenosine-induced hyperemia for each group. There was no significant difference in resting parameters between each group. During hyperemia, both men and women showed a significant increase in heart rate (HR), but only the women showed a significant rise in PRP, owing to a greater average increase in HR. There was no significant change in systolic, diastolic, or MBP from rest to stress in either group. Patients in both

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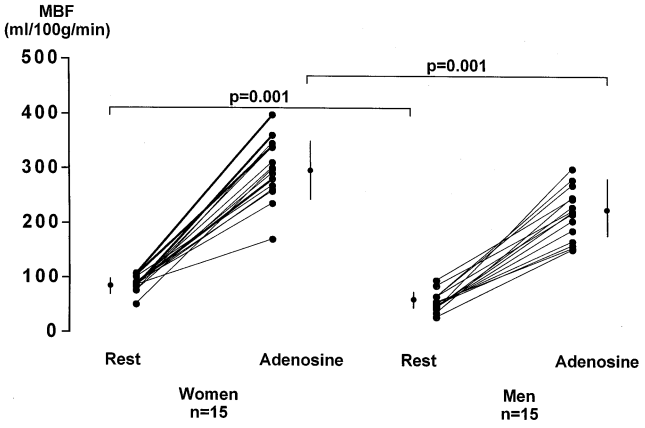

Figure 1. Myocardial blood flow (MBF) at rest and during adenosine hyperemia is plotted for women vs. men. Both groups show a significant rise in MBF during hyperemia, whereas values for women are significantly higher both at rest and during adenosine stress.

groups experienced similar symptoms in response to adenosine: flushing, shortness of breath, headache, and chest heaviness.

Visual and semiquantitative analysis of PET scans. One patient in each group had evidence of a regional perfusion abnormality by visual and semiquantitative analysis of PET images. One woman had a small, fixed lateral wall defect comprising less than 10% of the LCx vascular territory; this patient had undergone coronary angiography and had been shown to have normal coronary arteries, as well as normal left ventricular function by contrast ventriculography. The perfusion defect was not felt to be clinically relevant. Of the men, one patient had a reversible inferoposterior perfusion abnormality; however, the patient was asymptomatic and had a normal exercise single photon emission computed tomography (SPECT), and therefore coronary angiography was not performed. It is possible that this patient had an intermediate severity stenosis involving the right coronary or LCx coronary artery.

Quantitative myocardial blood flow analysis. The MBF values at rest and during adenosine-induced hyperemia are shown in Figure 1. Resting MBF in female patients was significantly higher than that of males. Blood flow in both patient groups increased significantly during adenosine-induced vasodilation (94 ± 22 to 296 ± 56 ml/100 g/min, $p < 0.0001$ for women; 72 ± 23 to 226 ± 47 ml/100 g/min, $p < 0.0001$ for men, Fig. 1). However, hyperemic MBF remained significantly lower in the male group than in the female group, as illustrated in Figure 1. Regional analysis of resting and hyperemic MBF revealed similar variability between vascular territories among men and women; there was no difference between the coefficient of variance obtained for the two groups for either resting or hyperemic blood flow.

Correlaton of risk factors and myocardial blood flow. None of the CAD risk factors documented in this patient population (positive family history, smoking, and hypertension) was a significant predictor of diminished hyperemic blood flow, and none correlated significantly with resting flow measurements.

Correlation of lipids and myocardial blood flow. Both total cholesterol level and lipid subfractions were compared with resting blood flow and hyperemic myocardial blood flow. The total cholesterol/HDL ratio and LDL/HDL ratio were also compared. No significant correlation was found between resting MBF and any lipid parameter, although the correlation with HDL levels approached statistical significance ($r = 0.32$, $p = 0.09$). As shown in Figure 2, stress MBF showed significant correlations to HDL level, Tg level, and cholesterol/HDL ratio. Hyperemic MBF showed the best correlation to Tg levels ($r = 0.48$, $p < 0.007$). No significant correlations were detected among total cholesterol levels, LDL levels, and LDL/HDL ratio and resting or stress blood flow.

Comparison of MBF and hemodynamics. As shown in Figure 3, both resting and hyperemic myocardial blood flow values correlated significantly with the respective HR values ($r = 0.50$, $p = 0.005$ for rest MBF; $r = 0.67$, $p < 0.0001$ for stress MBF). As a result of these HR correlations, MBF at rest also correlated with resting PRP, while hyperemic MBF correlated with stress PRP ($r = 0.56$, $p < 0.002$ for rest MBF; $r = 0.53$, $p < 0.002$ for stress MBF). The pharmacological effect of adenosine is reflected in the upward shift and steeper slope of the hyperemic blood flow correlations compared with correlations seen under resting conditions.

Multivariate linear regression. When all lipid parameters as well as gender, age, CAD risk factors, and HR were analyzed in multivariate fashion for their correlation to resting and stress myocardial blood flow, resting HR was the best predictor of resting MBF ($p = 0.003$), although HDL also remained a significant predictor ($p = 0.05$). For hyperemic MBF, gender was the strongest predictor ($p = 0.02$), followed by HDL ($p = 0.03$) and stress HR ($p = 0.04$). The LDL level showed a trend toward significance as a predictor of stress MBF ($p = 0.051$).

DISCUSSION

We sought to compare noninvasively measured resting and hyperemic myocardial blood flow (MBF) in a population of men and women of similar age, matched for cardiovascular risk factors and total cholesterol levels. Women differed from the men in that they had significantly higher HDL levels, and significantly lower Tg levels. The response to adenosine differed between men and women, in that our female patients exhibited a more marked heart rate (HR) response to adenosine. We found that the group of 15 females showed significantly higher resting as well as stress MBF than did their male

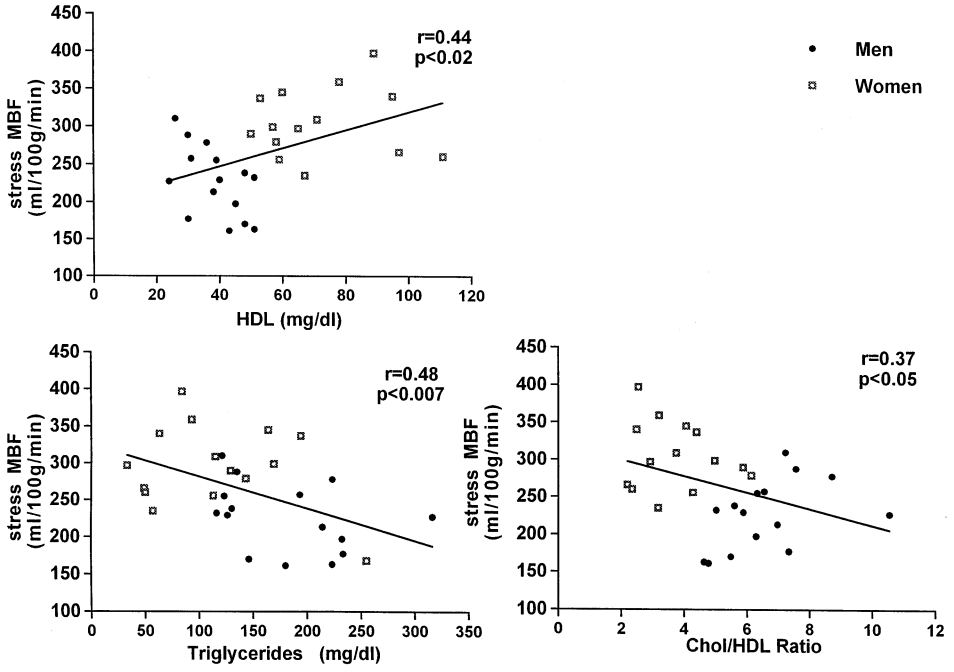

Figure 2. Correlations between stress myocardial blood flow (MBF) and lipid parameters HDL, triglycerides, and cholesterol/HDL ratio are plotted. Correlation coefficients and p values are as shown. To convert lipid values to millimoles per liter, multiply by 0.02586.

counterparts, and that these findings correlated with the lipid subfractions HDL and Tgs, which differed significantly between the two groups. We also found significant correlations between resting blood flow and HR as well as pressure rate product (PRP) at rest, and between hyperemic blood flow and stress HR and PRP. We found no differences in calculated myocardial flow reserve (stress MBF/resting MBF) between men and women. Thus, our study did not indicate that coronary vasodilator capacity differs between men and women.

Lipid effects. To our knowledge, this is the first reported comparison of myocardial blood flow responses between a cohort of women and of men with risk factors for coronary artery disease. Several differences became apparent when these women were compared with a matched male population; some

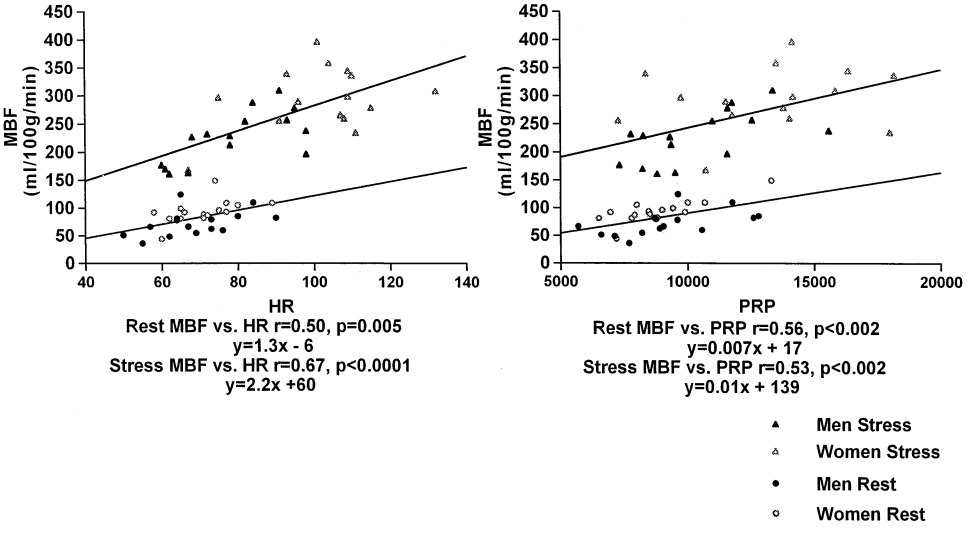

Figure 3. Correlations between myocardial blood flow (MBF) at rest and during stress and respective heart rate (HR) and pressure rate product (PRP) are shown. Stress correlations are depicted by **closed triangles** for men and **open triangles** for women. Resting correlations are depicted by **closed circles** for men and **open circles** for women. Correlation coefficients, p values, and equations for each correlation are as shown.

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were expected, and others unexpected. It is well known that women have a more favorable lipid profile in terms of risk factors for CAD than do men; a significant part of the observed gender gap in the heart disease prevalence between women and men is believed to be due to these lipid factors (14). Total cholesterol levels are believed to be as strong a predictor of CAD risk in women as in men, but HDL level is believed to be more closely correlated with CAD risk in women than in men (8).

In addition, elevated triglycerides may be a significant predictor of CAD risk in women to a greater extent than they are in men (15). Elevated Tgs may cause altered coronary blood flow on the basis of increased plasma viscosity; they may also be a marker for insulin resistance and thus for a predisposition to diabetes mellitus, which is known to be associated with impaired MBF (16). Our female population was postmenopausal; estrogen-replacement therapy, which can prevent the decline in HDL levels seen after menopause, and which may alter MBF, was being taken by only one woman in the study group.

Sex differences have also recently been reported in plaque morphology and the etiology of plaque rupture leading to coronary thrombosis (17,18). These investigators found that, whereas men most commonly developed thrombi due to rupture of lipid-rich plaques, women more commonly were found to develop intracoronary thrombi in areas of endothelial erosion, which occurred over plaques composed of smooth muscle cells and proteoglycans. Thus, the unfavorable lipid profile more commonly seen in men may be directly responsible for plaque vulnerability, whereas higher HDL levels and lower Tg levels as more commonly found in women may lead to alternate etiologies for coronary thrombosis, which presumably do not occur as frequently, and may also not respond to lipid-lowering therapy in the same manner (19).

Several recent studies have analyzed MBF using N-13 ammonia PET in a high-risk population (4,20). The findings reported by Dayanikli et al. (4), whose patient population consisted in part of the same patients used for the current study, applied only to men, and showed diminished hyperemic MBF and flow reserve in hypercholesterolemic men with additional risk factors for CAD. Furthermore, these investigators reported significant correlations among coronary flow reserve and total cholesterol, LDL cholesterol, and cholesterol/HDL ratio.

Yokoyama et al. (20) analyzed 14 men and 11 women with familial hypercholesterolemia and again found that both hyperemic myocardial blood flow and flow reserve were diminished in these patients when compared with a group of normal controls. They found statistically significant correlations between flow reserve and total cholesterol as well as LDL cholesterol levels. They also stratified both the control group and the familial hypercholesterolemics by gender, and showed higher stress MBF and flow reserve both in the female controls and the female hyperlipidemic patients; these differences were statistically significant only for flow reserve between male and female hyperlipidemic patients. The reasons for this difference remained largely unexplained; however, no gender difference was noted in their study in hemodynamic parameters or in lipid profiles.

Our study differs from these earlier reports in several ways. First, we studied an age- and cholesterol-matched group of women and men with additional risk factors for coronary artery disease who did not meet criteria for familial hyperlipidemia. Second, we found the expected gender differences in HDL and Tg levels between our patient groups, namely higher HDL and lower Tgs in women than in men. Importantly, we were able to show significant correlations between these lipid parameters and the hyperemic blood flow of the patients. Thus, we were able to confirm the postulated interaction between coronary reactivity and lipid levels seen by others (21).

Hemodynamic effects. Each group had equivalent resting HR and blood pressure, resulting in a similar PRP at rest. While both groups showed significant increases in HR during adenosine-induced hyperemia, the women showed a significantly greater rise in HR ($\Delta = 31$ for women vs. $\Delta = 10$ for men), resulting in a statistically significant increase in PRP with stress only for the female study group. This differential response could not be explained by heart-rate slowing medications, as none of the men and only two of the women were taking medications known to exert negative chronotropic effects. Neither group showed any significant change in blood pressure during adenosine hyperemia.

Previous studies undertaken to study hemodynamic response to adenosine infusion have also shown a significant rise in HR (22,23). However, in the face of maximal vasodilation, HR should not be expected to further increase MBF. Adenosine was believed to exert vasodilatory effects independently of its hemodynamic effects, which have been felt to be clinically insignificant for the most part (22). A HR-mediated augmentation of MBF has not been previously demonstrated. Indeed, McGinn et al. (24) showed that hyperemic blood flow did not change during pacing-induced increases in HR. We found that resting MBF correlated significantly with the resting PRP and resting HR, as has been shown by other investigators (6,24–26). The resting MBF was significantly higher in women than in men because of multiple factors. Although PRP was one component that correlated linearly with MBF, other factors including basal catecholamine levels, HDL levels, and HR (both of which were a significant predictor of resting MBF in multivariate analysis) also contributed to the resting blood flow. However, we also noted a correlation between HR (and, consequently, PRP) during adenosine-mediated vasodilation and hyperemic blood flow, a finding not shown in previous studies. This effect was entirely accounted for by the close correlation noted between HR during hyperemia and blood flow.

Analysis of our results shows that, while both HR and PRP correlated with hyperemic blood flow, the pharmacological effect of adenosine was reflected by the upward shift

and steeper slope of the hyperemic blood flow correlations compared with correlations seen under resting conditions. Dipyridamole acts as an indirect, and adenosine as a direct, coronary vasodilator; both agents thereby uncouple blood flow from oxygen demand and, consequently, from cardiac work (27). Exogenous adenosine exerts vasodilatory effects primarily on vascular smooth muscle cells, but it may also reflect endothelium-dependent vasorelaxant effects because hyperlipidemic patients presumably have impaired nitric oxide release, and thus compensatory increased basal adenosine levels, which may lead to a reduction in responsiveness to exogenous administration of the drug (28). Further interplay between endothelium-dependent and -independent adenosine-mediated effects can be related to the shear stress caused by vasodilatation, which elicits nitric oxide release from endothelial cells.

In the presence of impaired vasodilatory responses such as can be seen in hyperlipidemic patients, this vasorelaxant effect may be impaired (29). No studies have previously documented a gender-related difference in hemodynamic response to adenosine, and others have found no significant relationship between hyperemic blood flow and HR or PRP (25,30). In fact, because coronary blood flow occurs primarily during diastole, an increase in HR may actually result in a decrease in MBF because of reduced diastolic filling time. The increased HR response noted in women serves as a marker in the current study to support a differential pharmacologic effect of adenosine in women compared with men.

Possible mechanisms for our observations include a relatively greater catecholamine response to adenosine; perception of the infusion as a noxious stimulus could certainly lead to a catecholamine surge, which could be expected to exert several, potentially contradictory effects on MBF. Stimulation of myocardial $\alpha 1$ and $\alpha 2$ receptors would lead to coronary vasoconstriction and thus decrease MBF. However, stimulation of the relatively greater proportion of $\beta 1$ and $\beta 2$ receptors in the heart would lead to vasodilation and a positive chronotropic effect. This increased HR would lead to increased oxygen demand, and thus compensatory increased MBF, if the adenosine-induced vasodilation were less than complete. In a multicenter analysis of the safety profile of adenosine stress, Cerqueira et al. (23) showed that the risk of side effects during adenosine infusion was increased in women compared with men. Thus, if women experienced a differentially greater catecholamine surge in response to adenosine infusion than men, they might have an additional rise in MBF over and above the direct vasodilatory effect of the drug.

Study limitations. Significantly more men than women had a positive family history for CAD in our study population. This well-established risk factor for CAD could have contributed to the reduced stress MBF seen in the male cohort. However, family history was not significantly correlated with impaired hyperemic blood flow in our multivariate analysis. Our population was otherwise well-matched in terms of commonly accepted cardiovascular risk factors. Our patients did not routinely undergo cardiac catheterization, and thus CAD could not be absolutely ruled out in the majority of patients. However, any patient with symptoms that might be construed to be cardiac in origin did undergo coronary angiography; these patients were all found to have normal coronary arteries. Furthermore, all male patients underwent exercise or pharmacologic stress in conjunction with SPECT imaging to exclude significant disease, and PET images in all patients with the exception of one man and one woman showed no perfusion defects. Because rest-stress N-13 ammonia PET has been shown to have a high diagnostic accuracy in excluding coronary artery disease (31), coronary angiography was not believed to be indicated.

Our finding that the HR response to adenosine differed between men and women in the study most likely represents an epiphenomenon, as the hemodynamic difference did not account for the change in blood flow from rest to stress. To define MBF responses in our population more completely, these results should be compared with MBF measured in a normal male and normal female population. However, it is problematic to study women without risk factors for coronary disease, for these women will often be of child-bearing age, and will likely be unwilling to be subjected to unnecessary radiation exposure. Furthermore, these results do not reflect purely endothelium-dependent effects. Unfortunately, there currently is no single reliable noninvasive method for studying endothelium-dependent vasodilatation; use of the cold-pressor test is one possible modality that could be considered, although its effects are quite heterogeneous and difficult to standardize.

Conclusions. This study demonstrates gender differences in noninvasively assessed myocardial blood flow at rest and during hyperemia. Higher resting as well as hyperemic flow was detected in women with risk factors for coronary artery disease compared with age-matched men with similar risk-factor profiles. Myocardial blood flow correlated significantly with HDL levels and with Tg levels, and was also significantly correlated to HR and to pressure rate product. These findings may have implications for the use of adenosine hyperemia in study populations of mixed gender. Analysis of a sex-specific adenosine response requires further study; the potential role of estrogen and progesterone should also be investigated. Our findings support current pathophysiologic concepts that altered lipid profiles contribute significantly to the risk of CAD, and may provide additional insight into the delayed appearance of CAD in women.

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