

Mild Renal Insufficiency Is Associated With Angiographic Coronary Artery Disease in Women

Steven E. Reis, MD; Marian B. Olson, MS; Linda Fried, MD, MPH; Virginia Reeser, PA-C; Sunil Mankad, MD; Carl J. Pepine, MD; Richard Kerensky, MD; C. Noel Bairey Merz, MD; Barry L. Sharaf, MD; George Sopko, MD, MPH; William J. Rogers, MD; Richard Holubkov, PhD

Background—Mild renal insufficiency is associated with an increased risk for cardiovascular events in women with coronary artery disease (CAD). However, the relationship between mild renal insufficiency and atherosclerotic CAD in women is not known.

Methods and Results—Women with chest pain who were referred for coronary angiography in the NHLBI Women's Ischemia Syndrome Evaluation (WISE) study underwent quantitative coronary angiography, blood measurements of creatinine, lipids, and homocysteine, and assessment of CAD risk factors. Fifty-six women had mild renal insufficiency (serum creatinine 1.2 to 1.9 mg/dL), and 728 had normal renal function (creatinine <1.2 mg/dL). Creatinine correlated with angiographic CAD severity score ($r=0.11$, $P<0.004$) and maximum coronary artery stenosis ($r=0.11$, $P<0.003$). Compared with women with normal renal function, those with mild renal insufficiency were more likely to have significant angiographic CAD ($\geq 50\%$ diameter stenosis in ≥ 1 coronary artery) (61% versus 37%; $P<0.001$) and CAD in multiple vessels ($P<0.001$ for association) and had greater maximum percent diameter coronary stenosis ($59\pm 35\%$ versus $38\pm 36\%$; $P<0.001$). Mild renal insufficiency was associated with significant angiographic CAD independent of age and risk factors (OR=1.9, 95% CI=1.1 to 3.5). After controlling for homocysteine in 509 women, mild renal insufficiency remained predictive of CAD (OR=3.2, 95% CI=1.4 to 7.2).

Conclusions—In women with chest pain, mild renal insufficiency is an independent predictor of significant angiographic CAD. Mildly increased serum creatinine is probably a marker for unmeasured proatherogenic factors. (*Circulation*. 2002;105:2826-2829.)

Key Words: coronary artery disease ■ renal insufficiency ■ women

The prevalence of renal insufficiency is increasing in the United States. End-stage renal disease is associated with substantially increased mortality, primarily due to an increased risk of ischemic heart disease.¹ In postmenopausal women with preexisting coronary artery disease (CAD), mild to moderate renal insufficiency (serum creatinine ≥ 1.2 mg/dL) is associated with an increased risk for cardiovascular events.² The pathophysiological mechanism of this association may be related to progression of CAD, destabilization of atherosclerotic plaques, and/or coronary artery thrombosis. The present study is designed to evaluate the association between mild renal insufficiency and angiographic CAD in women.

Methods

Study Design

Women were enrolled in the Women's Ischemia Syndrome Evaluation (WISE) study if they were clinically referred for coronary

angiography to evaluate chest pain.³ All women provided written informed consent that was approved by the institutional review board at their local WISE site. Age and self-reported CAD risk factors were recorded at study entry. Quantitative coronary angiography was performed.⁴ Women with 1 or more $\geq 50\%$ diameter stenosis were classified as having "significant" CAD, those with maximum stenosis of 20% to 50% had "minimal" CAD, and women with <20% stenoses in all coronary arteries had "no CAD." CAD severity score was calculated by a modified Gensini index.⁴

Laboratory Testing

Serum creatinine was measured using standard technique in the clinical laboratory at each site. For secondary analysis, creatinine clearance (mL/min) was estimated by the Cockcroft-Gault equation: Creatinine clearance = $(0.85 \times [140 - \text{age}(\text{years})] \times \text{weight}(\text{kg}) / [\text{serum creatinine}(\text{mg/dL}) \times 72])$.

Lipids were measured in fasting blood plasma at the WISE lipid core laboratory (Cedars Sinai Medical Center, Los Angeles, Calif).⁵ Plasma homocysteine levels were measured at the University of

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From the Cardiovascular Institute (S.E.R., V.R.), the Department of Epidemiology (M.B.O., R.H.), and the VA Pittsburgh Healthcare System Department of Medicine (L.F.), University of Pittsburgh, Pittsburgh, Pa; Division of Cardiology (S.M.), MCP-Hahnemann School of Medicine, West Penn-Allegheny Health System, Pittsburgh, Pa; Division of Cardiology (C.J.P., R.K.), University of Florida, Gainesville, Fla; Division of Cardiology (C.N.B.M.), Cedars-Sinai Medical Center, Los Angeles, Calif; Division of Cardiology (B.L.S.), Rhode Island Hospital, Providence, RI; Division of Heart and Vascular Diseases (G.S.), National Heart, Lung, and Blood Institute, Bethesda, Md; and Division of Cardiology (W.J.R.), University of Alabama at Birmingham.

Correspondence to Steven E. Reis, MD, University of Pittsburgh Medical Center, 200 Lothrop St, Pittsburgh, PA 15213. E-mail reisse@msx.upmc.edu
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TABLE 1. Baseline Characteristics of Women Stratified by Creatinine

Creatinine, mg/dL	<1.2	1.2 to 1.9	<i>P</i>
n	728	56	
Age, y	58±11	62±11	0.014
Cholesterol, mg/dL			
Total	196±45	191±46	NS
High-density lipoprotein	54±13	52±10	NS
Low-density lipoprotein	112±39	106±43	NS
Triglycerides, mg/dL	156±125	166±85	NS
Systolic blood pressure, mm Hg	135±20	142±21	0.022
Diastolic blood pressure, mm Hg	76±11	77±11	NS
Fasting glucose, mg/dL	114±51	131±84	NS
Body-mass index, kg/m ²	30±6.5	30±6.5	NS
Homocysteine, μmol/L	7.8±4.0	11.1±4.7	<0.001
History, %			
Hypertension	58	73	0.025
Diabetes	23	41	0.002
Current cigarette smoking	19	18	NS
Dyslipidemia	53	64	NS
Postmenopausal	75	88	0.040
Current postmenopausal HRT	48	35	NS
Current, %			
β-Blocker	39	46	NS
ACE or ARB	27	59	<0.01
Calcium antagonist	27	30	NS
Aspirin	61	73	NS
Statin	25	38	<0.04

Data are expressed as mean±SD. NS indicates nonsignificant; HRT, hormone replacement therapy; ACE, angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.

Pittsburgh in the last consecutive 509 women. Samples and standards were treated with sodium borohydride (Sigma) and monobromobimane (Thiolyte Reagent, Calbiochem). Thiobimane adducts were quantified by high-performance liquid chromatography with fluorescence detection (Waters). Results are linear in the range of 3.5 to 53.5 μmol/L. Coefficients of variation were 2.4% to 3.1% within run and 6.4% to 7.8% between runs.

Statistical Analysis

This report includes 728 women with normal renal function (creatinine <1.2 mg/dL) and 56 with mild renal insufficiency (creatinine 1.2 to 1.9 mg/dL). Associations between continuous variables were evaluated using Spearman rank correlation coefficients. Comparisons by creatinine as a dichotomous variable were performed using the Wilcoxon 2-sample and chi-square tests for continuous and discrete measures, respectively. Associations of outcomes with ordered categorical variables were assessed using the Mantel-Haenszel chi-square test. After univariate associations of creatinine, demographics, and risk factors with CAD were evaluated, logistic regression was used to model the probability of significant CAD as a function of creatinine (<1.2 versus 1.2 to 1.9 mg/dL). Univariate

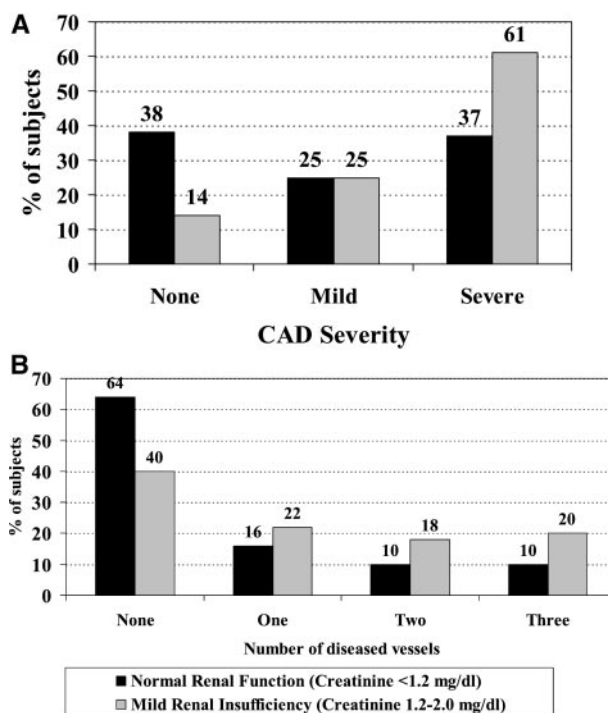


Figure 1. Prevalence of (A) CAD severity ($P=0.001$) and (B) multivessel CAD ($P=0.004$) in women with and without mild renal insufficiency classified by creatinine.

associations of variables listed in Table 1 with CAD were evaluated. After examination of goodness-of-fit statistics, the variable showing the strongest association was entered into a forward-step regression model (level for entry, $P=0.05$). Additional variables were entered and the effect was examined at each step. The Hosmer-Lemeshow test was used to examine lack of fit in the final model. Similar analyses were performed using estimated creatinine clearance (normal:creatinine clearance >80 mL/min [$n=473$]; mild renal insufficiency:creatinine clearance 50 to 80 mL/min [$n=248$]). Values of $P\leq 0.05$ were considered significant.

Results

Baseline Characteristics

Characteristics of women with normal renal function and mild renal insufficiency are presented in Table 1. Women with mild renal insufficiency were older, had higher systolic blood pressure, and greater prevalences of hypertension, diabetes, and menopause.

Association Between Creatinine and Angiographic CAD

Creatinine correlated with the angiographic severity score ($r=0.11$, $P<0.004$) and maximum percent diameter coronary artery stenosis ($r=0.11$, $P<0.003$). Creatinine also correlated with age ($r=0.18$, $P<0.001$), triglycerides ($r=0.08$, $P<0.05$), systolic blood pressure ($r=0.09$, $P<0.01$), and homocysteine ($r=0.18$, $P<0.001$). The prevalence of significant angiographic CAD was greater in women with mild renal insufficiency than in those with normal renal function (Figure 1A, $P=0.001$). Those with mild renal insufficiency were more likely to have significant multivessel CAD (Figure 1B, $P=0.004$), a greater maximum percent diameter coronary stenosis ($59\pm 35\%$ versus $38\pm 36\%$; $P<0.001$), and a higher

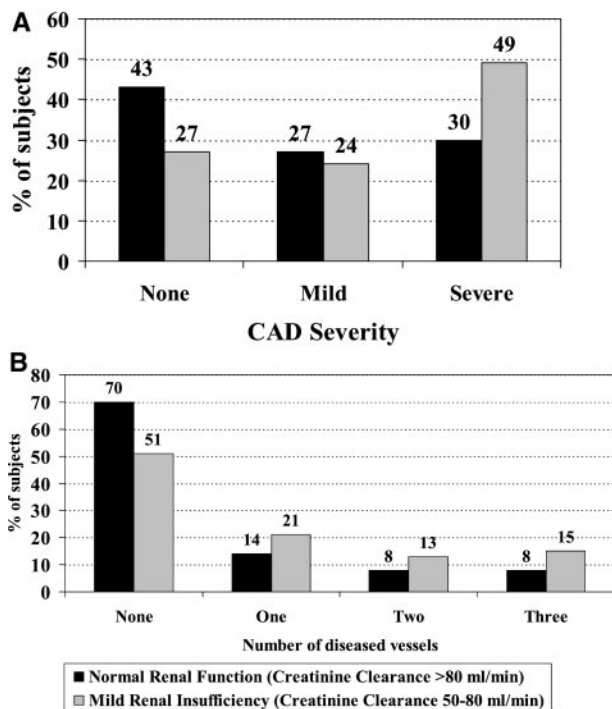


Figure 2. Prevalence of (A) CAD severity ($P=0.001$) and (B) multivessel CAD ($P=0.001$) in women with and without mild renal insufficiency classified by creatinine clearance.

angiographic severity score (22 ± 19 versus 14 ± 14 ; $P<0.001$). Similar findings were noted when creatinine clearance was used to classify renal function (Figure 2).

Mild Renal Insufficiency as an Independent Predictor of Angiographic CAD

In univariate analysis, women with mild renal insufficiency were 2.6 times more likely to have significant CAD than those with normal renal function (95% confidence interval [CI]=1.5 to 4.6). Other univariate predictors of significant CAD include hypertension (odds ratio [OR]=1.9, 95% CI=1.4 to 2.5), diabetes (OR=3.3, 95% CI=2.4 to 4.6), dyslipidemia (OR=2.7, 95% CI=2.0 to 3.7), menopause (OR=2.1, 95% CI=1.5 to 3.1), and age (per 10 years) (OR=1.7, 95% CI=1.5 to 2.0). Postmenopausal hormone replacement therapy was a negative predictor of CAD (OR=0.6, 95% CI=0.5 to 0.8). Logistic modeling controlled for total and LDL-cholesterol, systolic and diastolic blood pressures, age, diabetes, hypertension, cigarette smoking, dyslipidemia, and menopause. This demonstrated that mild renal insufficiency was associated with a 1.9-fold risk of significant angiographic CAD (95% CI=1.1 to 3.5) (Table 2). Similar findings were noted when using creatinine clearance to define renal function; creatinine clearance 50 to 80 mL/min was associated with a 1.5-fold risk of significant CAD (95% CI=1.1 to 2.3) independent of other factors.

End-stage renal disease is associated with increased circulating levels of homocysteine, which is independently associated with cardiovascular risk.⁶ After controlling for homocysteine in logistic regression analysis, mild renal insufficiency remained an independent predictor for significant CAD (OR=3.2, 95% CI=1.4 to 7.2).

TABLE 2. Logistic Regression Model Evaluating Independent Predictors of Significant Angiographic CAD in Women With Chest Pain (c index=0.747)

Variable	Odds Ratio	95% CI	P
Age, per 10 y	1.7	1.5 to 2.0	<0.001
Mild renal insufficiency, creatinine 1.2 to 1.9 mg/dL	1.9	1.1 to 3.5	0.032
Diabetes	2.7	1.8 to 3.8	<0.001
Dyslipidemia	2.2	1.6 to 3.0	<0.001
Current HRT	0.7	0.5 to 0.9	<0.007

CI indicates confidence interval; HRT, hormone replacement therapy.

Discussion

Our results are the first to demonstrate that mild renal insufficiency is an independent predictor for significant angiographic CAD in women with chest pain. These results extend observations that declining renal function is associated with subclinical atherosclerosis (vascular stiffness, brachial artery endothelial dysfunction, carotid artery intima-media thickening).⁷⁻⁹ They also offer biological rationale for the previously reported finding that mild-moderate renal insufficiency (creatinine ≥ 1.2 mg/dL) is associated with an increased risk for cardiovascular events in women with CAD.²

The pathophysiological mechanism for the association between mild renal insufficiency and angiographic CAD is uncertain. Circulating creatinine is not likely to be proatherogenic but is probably a marker for other factors that promote atherosclerosis. Because our reported association between mild renal insufficiency and angiographic CAD was found to be independent of traditional risk factors and homocysteine, it is likely that mild renal insufficiency is associated with nontraditional proatherogenic factors.

Renal dysfunction is associated with a systemic proinflammatory state; circulating levels of proinflammatory cytokines are increased in renal insufficiency.^{10,11} Cytokines have been isolated in atherosclerotic lesions and are associated with an increased cardiovascular risk.^{12,13} Cytokines also stimulate hepatic production of acute-phase reactants (eg, C-reactive protein) whose levels predict cardiovascular mortality in patients with end-stage renal disease.¹⁴ Therefore, proinflammatory cytokines may modulate cardiovascular risk in patients with renal dysfunction. Future WISE analyses will evaluate the association between mild renal insufficiency, inflammatory mediators, and atherosclerosis. Additional studies need to investigate other effects of renal insufficiency (eg, oxidative stress, increased advanced glycation end-products, changes in apoproteins) as potential mechanisms for the association between mild renal insufficiency and angiographic CAD.

Limitations

Our results are consistent with and extend previous associations between mild renal insufficiency and subclinical atherosclerosis.⁷⁻⁹ However, generalization of our results from a female cohort with chest pain to the population at large is limited. The association between renal insufficiency and cardiovascular pathophysiology may be gender-dependent. Also, our subjects had clinically-indicated coronary angio-

raphy to evaluate chest pain, which may result in a referral bias. Despite these limitations, our study allowed us to investigate the association between renal function and angiographic CAD because it included a large cohort of women that underwent quantitative coronary angiography and rigorous analysis of CAD risk factors. Finally, we used serum creatinine and estimated creatinine clearance to classify renal function. Although these methods may be less accurate than measurement of creatinine clearance, they represent measures that are most commonly used in clinical practice.

Conclusions

Our results demonstrate that mild renal insufficiency is associated with significant angiographic CAD in women with chest pain. This association is independent of traditional CAD risk factors and homocysteine levels. We postulate that mild renal insufficiency is a marker for nontraditional risk factors that modulate atherogenesis. Future studies need to evaluate the pathophysiological mechanism of this finding and the long-term predictive value of mild renal insufficiency for cardiovascular events in women with chest pain.

Acknowledgments

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