

Association between Renal Insufficiency and Inducible Ischemia in Patients with Coronary Artery Disease: The Heart and Soul Study

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Abstract. Chronic renal insufficiency (CRI) is a predictor of stroke, cardiovascular, and all-cause mortality, but the mechanisms responsible for these associations are unclear. Whether CRI was associated with severity of coronary artery disease (CAD) as measured by exercise stress echocardiography among outpatients with stable CAD was evaluated. This study is a cross-sectional analysis of the Heart and Soul study, a prospective cohort of patients with known CAD. Renal function was assessed by 24-h urine collection, and CRI was defined as measured creatinine clearance ≤ 60 ml/min. Exercise stress echocardiography was used to identify inducible ischemia, defined as any wall motion abnormality seen at stress but not at rest. Logistic regression was used to evaluate the association of CRI with exercise-induced ischemia after adjustment for cardiovascular risk factors. Participants with CRI composed 97 (23%) of the 431 participants and were charac-

terized by older age, worse CAD, lower ejection fraction, greater left ventricular mass and higher C-reactive protein values. The prevalence of exercise-induced ischemia was also substantially greater in the participants with CRI (42% versus 23%; odds ratio [OR], 2.3; 95% confidence interval [CI], 1.4 to 3.8; $P < 0.001$). This association was minimally changed by adjustment for traditional cardiovascular risk factors and coronary disease history (OR, 2.0; 95% CI, 1.3 to 3.3; $P < 0.01$) and remained strong even after adjustment for C-reactive protein (OR, 2.3; 95% CI, 1.0 to 5.1; $P = 0.04$). CRI is strongly associated with exercise-induced ischemia in patients with CAD. The greater severity of atherosclerotic disease observed in patients with CRI may in part explain the association of CRI with increased cardiovascular risk among individuals with CAD.

Mild to moderate chronic renal insufficiency (CRI) is estimated to affect more than one fourth of people aged 65 and older in the United States (1) and is an independent predictor of stroke (2,3), cardiovascular (2–6), and all-cause mortality (2–5,7,8). In people with established coronary artery disease (CAD), CRI predicts recurrent events as strongly as other established cardiovascular risk factors such as diabetes and elevated BP (6). Whether the cardiovascular risk in the setting of CRI is due to increased atherosclerotic burden, higher risk of plaque rupture as a result of inflammation (9), or other mechanisms is unknown.

One method that can be used to determine the severity of CAD is exercise treadmill testing with stress echocardiography (10–12). To evaluate the association of CRI and inducible

ischemia, we measured creatinine clearance (CrCl) and performed stress echocardiography in a cross-sectional study of 431 participants enrolled in the Heart and Soul study. We hypothesized that CRI would be associated with inducible ischemia independent of hypertension, diabetes, or other traditional cardiovascular risk factors. Because inflammatory biomarkers are known to be elevated in people with CRI, we also sought to determine whether inflammation was a mediator of this association (9).

Materials and Methods

Participants

The Heart and Soul study is a prospective cohort designed to investigate the influence of psychosocial factors on CAD progression. Methods have been described previously (13,14). Participants were recruited from outpatient clinics in the San Francisco Bay Area if they met one of the following inclusion criteria: (1) history of myocardial infarction, (2) angiographic evidence of $>50\%$ stenosis in one or more coronary vessels, (3) evidence of exercise-induced ischemia by treadmill or nuclear testing, (4) history of coronary revascularization, or (5) documented diagnosis of CAD by an internist or cardiologist. Participants were excluded when they were not able to walk one block or were likely to move out of the area within 3 yr. The study protocol

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was approved by the appropriate Institutional Review Boards, and all participants provided written, informed consent.

Between September 2000 and March 2002, 564 participants were enrolled. We excluded those who did not have 24-h urine collection data ($n = 7$) or who were unable to perform at least 3 min of exercise by the Bruce protocol ($n = 126$). This was done to ensure that a minimum level of exertion was attained to assess stress-induced ischemia. The study population therefore includes 431 participants.

Measurements

Primary Predictor Variable. Presence or absence of CRI was determined by 24-h urine collection for all participants. At the intake appointment, participants were provided with a 3-L collection jug and instructed to save all urine between the end of their intake appointment and the time when a researcher recovered the urine. Participants were instructed to keep the urine collections refrigerated at all times. Research personnel arrived at the participants' home 24 h after their inception appointments to ensure accurately timed specimens. At that time, participants were asked about the time of their first and last voids. When more than 1 h had passed since their last void, participants were instructed to void at that time to complete the collection. All participants were asked whether they were able to collect all urine or whether some fraction had been inadvertently discarded. When the sample was reported to be incomplete, participants were asked to repeat the collection, and research personnel returned 24 h later to re-collect the urine. When the 24-h urine volume was <1 L, participants were asked to repeat the collection to ensure an adequately collected specimen. Similarly, when the 3-L collection jug was completely full, participants were given two new jugs and asked to repeat the collection to ensure that no urine was inadvertently discarded. When participants were unable to collect all urine for any reason or had urinary incontinence, their samples were deemed inadequate and no data were recorded for these participants. CrCl was calculated using the following formula: urine creatinine (mg/dl) * 24-h urine volume (dl)/serum creatinine (mg/dl) * 1440 (min/d). *A priori*, we defined CRI as measured CrCl of ≤ 60 ml/min (15).

Secondary Predictor Variables. Age; race; smoking status; and medical history of diabetes, hypertension, myocardial infarction, and coronary revascularization were determined by self-report. We measured weight and height and calculated body mass index (kg/m^2). Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. After a 12-h fast, serum samples were obtained for measurement of creatinine, total cholesterol, HDL, LDL, albumin, and hematocrit.

To explore the role of inflammation as a potential mediator of the association between CRI and ischemia, we measured C-reactive protein (CRP) in 118 participants with exercise-induced ischemia and in a random sample of 111 participants without ischemia. We used the Roche Integra assay, an enhanced immunoturbidimetric assay that uses latex particles that are coated with monoclonal anti-CRP antibodies to measure CRP with high sensitivity. The assay has been standardized against the World Health Organization reference and has been compared with the Dade nephelometric method with a correlation coefficient of 0.997. The interassay coefficient of variation is 3.2%, and the lowest detectable measurement with this assay is 0.025 mg/dl. For this analysis, we considered high CRP levels as >0.38 mg/dl, based on cut points used in previous studies (13,16).

Outcome Variable. The primary outcome was the presence or absence of exercise-induced ischemia (17). We performed a symptom-limited graded exercise treadmill test according to the Standard Bruce Protocol for all participants at their inception appointment. Participants were asked to walk on a treadmill beginning at a workload of 20 to 30 W and increased by 20 to 30 W every 3 min until they reached dyspnea, symptom-limited fatigue, chest discomfort, or electrocardiographic changes suggestive of ischemia. Continuous electrocardiographic monitoring with 12-lead electrocardiography was performed throughout exercise.

Doppler echocardiography just before exercise was used to obtain a complete resting two-dimensional echocardiogram, including imaging and Doppler in all standard views and subcostal imaging of the inferior vena cava. Standard two-dimensional parasternal short-axis and apical two- and four-chamber views obtained during held inspiration were planimeted using a computerized digitization system (Tom Tec Corporation, Boulder, CO) to determine left ventricular volume, ejection fraction, stroke volume, cardiac output, and mass. At peak exercise, apical two- and four-chamber views were obtained to detect the development of right or left ventricular dilation or wall motion abnormalities. We defined exercise-induced ischemia as the presence of new wall motion abnormalities not visualized on the baseline rest echocardiogram. An experienced echocardiographer who was without knowledge of electrocardiograms, renal function status, or additional diagnostic tests analyzed all echocardiograms.

Statistical Analyses

Differences in baseline characteristics between participants with and without CRI were compared using χ^2 tests for dichotomous variables and t tests (or nonparametric equivalent) for continuous variables. We used forward stepwise multivariate logistic regression to determine the independent association of CRI with exercise-induced ischemia. Certain variables were forced into the multivariate model because of their strong association with cardiovascular or renal disease in previous studies (age, diabetes, hypertension, angiotensin-converting enzyme inhibitor use, HDL, and LDL). Other candidate variables that were associated with exercise-induced ischemia at $P < 0.2$ were also retained in our multivariate models. Candidate variables included gender; race; history of congestive heart failure, myocardial infarction, angioplasty, coronary bypass surgery, angina, or smoking status; ejection fraction, left ventricular mass, body mass index, serum levels of total cholesterol, triglycerides, hematocrit, and albumin; and medical therapy with HMG-CoA reductase inhibitors, aspirin, and β blockers. Finally, to determine whether inflammation attenuates the association between CRI and ischemia, we performed further multivariate adjustment for CRP in the subset of participants for whom CRP values were available. Analyses were performed using the Statistical Analysis Software (version 8; SAS Institute, Inc, Cary, NC).

Results

Baseline Characteristics

Among the 431 participants, 97 (23%) had CRI. Of these, 68 participants had CrCl between 40 and 60 ml/min, 27 participants had CrCl between 20 and 40 ml/min, and two participants had CrCl <20 ml/min. Compared with participants who had normal renal function, those who had CRI were older and more often had a history of myocardial infarction or coronary

artery bypass surgery (Table 1). They had a lower mean ejection fraction and greater left ventricular mass. Participants with CRI also had lower body mass index, hematocrit, and albumin levels and higher CRP measurements. They were more likely to be taking statins and less likely to be taking aspirin.

Association of Renal Insufficiency and Exercise-Induced Ischemia

CRI was strongly associated with exercise-induced ischemia (Figure 1, Table 2). Among participants with CRI, 42% had inducible ischemia, compared with 23% of those with normal renal function (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.4 to 3.8; *P* < 0.01). After multivariate adjustment, CRI remained strongly associated with exercise-induced ischemia (OR, 2.0; 95% CI, 1.2 to 3.3; *P* =

0.01). After further adjustment for CRP, the adjusted association was essentially unchanged (OR, 2.3; 95% CI, 1.0 to 5.1).

Test for Interaction

In stratified analysis, we observed similar associations between CRI and inducible ischemia in participants with and without diabetes (*P* = 0.67 for interaction). The OR for CRI as a predictor of exercise-induced ischemia was 2.7 (95% CI, 1.1 to 7.1) in participants with diabetes and 2.1 (95% CI, 1.2 to 3.7) in those without diabetes. Similarly, there was no interaction with hypertension. The odds of CRI as a predictor of ischemia was 2.3 (95% CI, 1.2 to 4.3) for participants with hypertension and 1.7 (0.6 to 4.6) in those without hypertension (*P* 0.93 for interaction). Likewise, we did not observe any significant interactions between CRI

Table 1. Baseline characteristics of the 431 participants by presence of chronic renal insufficiency

Variable	Creatinine Clearance		P Value
	≥60 ml/min (n = 334)	<60 ml/min (n = 97)	
Age	67 ± 10.4	72 ± 9.2	<0.001
Male	90%	92%	0.57
Race			
white	61%	63%	0.71
black	13%	12%	0.90
other	26%	25%	0.75
Medical history			
hypertension	65%	75%	0.07
diabetes	20%	26%	0.23
CHF	15%	22%	0.09
myocardial infarction	54%	70%	0.01
angioplasty	44%	51%	0.27
CABG	41%	53%	0.03
angina	61%	68%	0.19
current smoker	16%	14%	0.67
LV ejection fraction	0.63 ± 0.10	0.59 ± 0.11	<0.01
LV mass	185 ± 55	198 ± 64	0.04
Body mass index	28 ± 4	27 ± 4	0.02
Serum measurements			
total cholesterol	178 ± 41	172 ± 39	0.15
LDL	103 ± 32	100 ± 30	0.48
HDL	47 ± 14	46 ± 16	0.60
triglycerides	154 ± 175	124 ± 60	0.10
hematocrit	41 ± 4	39 ± 4	<0.01
albumin	4.0 ± 0.3	3.8 ± 0.4	<0.01
CRP levels (median)	1.4	2.3	0.04
high CRP (>0.38 mg/dl)	19%	29%	0.14
Medications			
ACE inhibitor or ARB	29%	31%	0.76
statin	40%	54%	0.01
aspirin	85%	75%	0.03
β blocker	55%	57%	0.74

CHF, congestive heart failure; CABG, coronary artery bypass surgery; LV, left ventricular; CRP, C-reactive protein; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

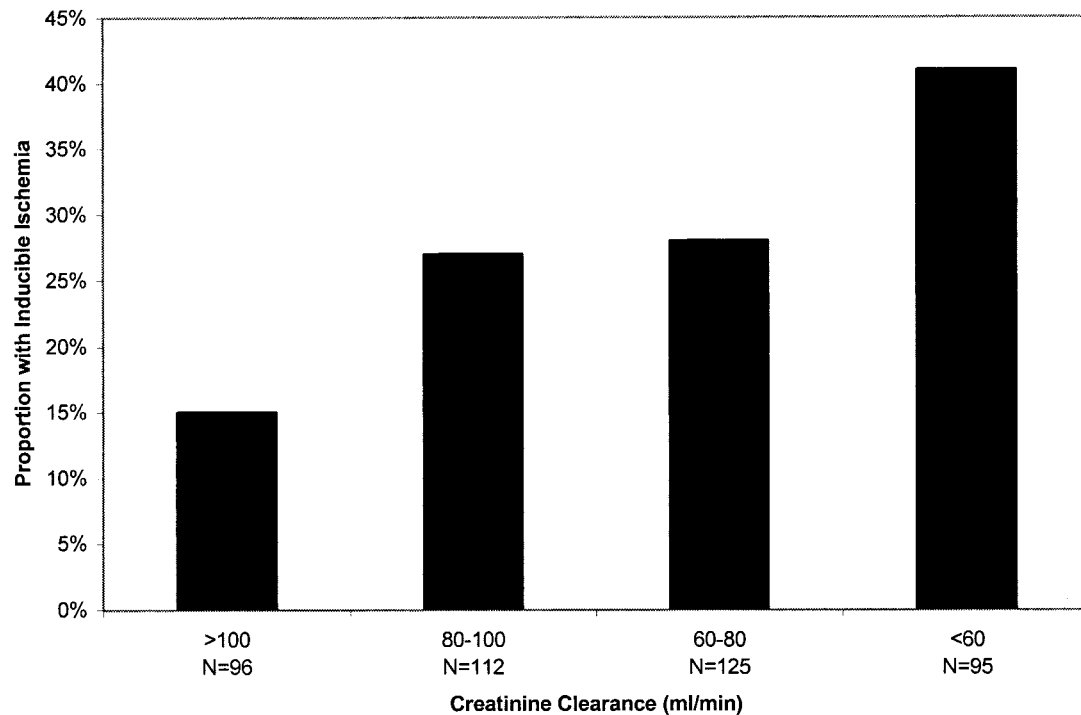


Figure 1. Percentage of participants with inducible ischemia by subgroup of measured creatinine clearance. The prevalence of inducible ischemia increased significantly as creatinine clearance decreased ($P < 0.001$ for trend).

Table 2. Univariate and multivariate association of chronic renal insufficiency with exercise-induced ischemia

	No. with Ischemia with Normal Renal Function	No. with Ischemia with CRI	Odds Ratio	95% CI	<i>P</i> Value
Unadjusted analysis ($n = 431$)	79	39	2.3	1.4–3.8	<0.01
Adjusted analysis ^a ($n = 409$)	—	—	2.0	1.2–3.3	0.01
Adjusted analysis ^a including CRP ^b ($n = 190$)	59	31	2.3	1.0–5.1	0.04

^a Adjusted for age, diabetes, hypertension, ACE inhibitor/ARB use, history of myocardial infarction, serum HDL and LDL levels, history of angioplasty, and history of coronary bypass graft surgery.

^b Includes 118 participants with inducible ischemia and 111 randomly selected participants without inducible ischemia.

and levels of hematocrit ($P = 0.31$ for interaction), CRI and congestive heart failure ($P = 0.30$ for interaction), or CRI and elevated CRP ($P = 0.25$ for interaction).

Discussion

Our analysis demonstrates that CRI is strongly associated with exercise-induced ischemia as assessed by stress echocardiography in participants with established CAD. The association was substantial and independent of other known risk factors such as hypertension or diabetes. As stress echocardiograms have been shown to predict CAD risk and atherosclerotic burden (10–12), our findings indicate that even among participants with known CAD, the presence of CRI is associated with increased atherosclerosis. These results add to the growing body of evidence suggesting that CRI predicts high cardiovascular risk in individuals with established CAD (4–6).

The increased cardiovascular risk for individuals with CRI was explained only in part by their increased prevalence and severity of diabetes and hypertension. Other renal-specific mechanisms likely contribute to the increased risk and are poorly understood. The proinflammatory state described in CRI has been proposed as one potential mediator (9). The current analysis, along with previous work from our group (9), establishes that CRP levels are elevated in individuals with CRI. However, CRP did not seem to substantially mediate the association of CRI with inducible ischemia in this study. Multiple other factors have also been proposed, including elevated levels of fibrinogen (9) and homocysteine (18), altered lipid metabolism (19–21), and markers of increased coagulability and fibrinolysis (9). Their relative contributions should be addressed in future studies.

The findings of our study indicate that individuals with stable CAD and CRI may benefit from more aggressive car-

diovascular screening and prevention. We found that individuals at particularly high risk can be identified with stress echocardiography, a noninvasive test readily available at most medical centers. Individuals with inducible ischemia might benefit from more intensive medical therapy for established and modifiable cardiovascular risk factors. The importance of such therapy is reinforced by multiple previous studies that have shown that use of cardioprotective medications is lower in individuals with CRI than in those with normal renal function (7,22).

A particular strength of our study is the use of a direct measure of renal function with 24-h urine collections. Most previous studies have relied on one-time measurements of serum creatinine to estimate CrCl. We believe that our study therefore more accurately quantifies the association of CRI with inducible ischemia and CAD risk. However, several limitations should also be considered in interpreting our results. Although our findings demonstrate that CRI is associated with exercise-induced ischemia, we cannot determine the direction of the association because of the cross-sectional design. In addition, although our hypothesis is that CRI leads to accelerated atherosclerosis and coronary disease instability, it is possible that an unmeasured risk factor was a predictor of both CRI and exercise-induced ischemia. However, to explain the twofold odds of the observed association, any lurking confounder would need to be highly prevalent in the cohort and strongly associated with both CRI and inducible ischemia. Furthermore, our study participants were mostly men, and our results therefore may not be generalizable to women. Finally, our study did not include anatomic measures of coronary disease; thus, we were not able to determine whether CRI is associated with ischemia because of greater anatomic disease burden or through other mechanisms (23,24,25).

In summary, we found that among individuals with CAD, the presence of CRI is strongly associated with exercise-induced ischemia. We believe that all patients with CRI merit aggressive cardiovascular risk factor management. Those with exercise-induced ischemia are likely at highest risk and might be considered for further diagnostic investigation. Finally, although we found individuals with CRI to have higher CRP values, the association of CRI with inducible ischemia did not seem to be mediated solely through inflammation.

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ERRATUM

In the December 2003 issue of *JASN*, the reference list in the following article was published in the incorrect order:

Ix JH, Shlipak MG, Liu HH, Schiller NB, Whooley MA: Association between renal insufficiency and inducible ischemia in patients with coronary artery disease: The Heart and Soul Study. *J Am Soc Nephrol* 14: 3233–3238, 2003

The publisher regrets the error. A corrected reference list is printed below.

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