

# Impact of Renal Function on Coronary Plaque Morphology and Morphometry in Patients With Chronic Renal Insufficiency as Determined by Intravascular Ultrasound Volumetric Analysis

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The aim of the present study was to use intravascular ultrasonography (IVUS) to assess plaque morphology and morphometry in patients with varying degrees of chronic renal insufficiency, including end-stage renal disease (ESRD) on dialysis replacement. Cardiovascular disease is the main cause of death for patients with chronic renal insufficiency, particularly in patients with ESRD. The impact of several degrees of renal insufficiency (including ESRD) on coronary plaque characteristics has not been determined. A total of 142 patients who underwent IVUS imaging of a de novo native coronary artery stenosis before percutaneous intervention were matched for age, gender, and diabetes and were grouped according to calculated creatinine clearance (CrCl): CrCl >70 ml/min (n = 39); CrCl 50 to 69 ml/min (n = 41); CrCl <50 ml/min, (n = 37), and ESRD (n = 25). Standard clinical, angiographic, and IVUS parameters were measured. The ESRD group had more African-American (p = 0.002) and hypertensive (p = 0.002) patients. No significant difference was found in any of the IVUS measurements among patients with CrCl >70, 50 to 69, and <50 ml/min: reference and lesion site arterial, lumen, and plaque areas and volumes, and arterial calcium (p = NS for all comparisons). Conversely, patients with ESRD had larger reference segment arterial and lumen areas and volumes; larger lesion site arterial, lumen, and plaque areas; and larger arcs of calcium (p <0.05 for all post hoc comparisons between patients with ESRD and patients with CrCl >70, 50 to 69, and <50 ml/min). Thus, chronic renal insufficiency in the absence of dialysis is not associated with increased reference segment or lesion site plaque burden and calcium. However, the transition to the need for dialysis is associated with progressive calcific atherosclerosis (larger lesion plaque area and calcium). © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96:892–896)

Few nonangiographic assessments of coronary artery disease have been performed in patients with chronic renal insufficiency (CRI).<sup>1–7</sup> Previous studies with electron-beam computed tomography have demonstrated that coronary and vascular calcific deposits are common and usually severe in these patients.<sup>8–13</sup> Coronary artery calcium is a sensitive marker of underlying atherosclerosis and has been associated with cardiovascular events in patients without renal disease.<sup>11</sup> Intravascular ultrasound (IVUS) can provide high-resolution and high-quality structural information of the coronary arteries in vivo.<sup>14</sup> The objectives of the present study were to assess IVUS plaque morphology and mor-

phometry in patients with varying degrees of CRI, including those with end-stage renal disease (ESRD) on dialysis replacement therapy, and to determine the extent of coronary artery calcium in this patient population.

## Methods

**Patient population:** The study population consisted of 142 patients who underwent IVUS examination of a de novo native coronary artery stenosis before percutaneous coronary intervention at the Washington Hospital Center (Washington, DC). These patients were matched for age, gender, and the presence of diabetes and were then grouped according to the calculated creatinine clearance (CrCl) using previously established categories<sup>7,8</sup>: CrCl ≥70 ml/min (n = 39); CrCl 50 to 69 ml/min (n = 41); CrCl <50 ml/min (n = 37), and ESRD on dialysis replacement therapy (n = 25). CrCl was calculated applying the Cockcroft-Gault formula<sup>15</sup> using the baseline serum creatinine:  $\text{CrCl} = ([140 - \text{age}] \times \text{weight/serum creatinine} \times 72)$ , with female gender

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Table 1  
Baseline clinical characteristics

Variable	CrCl (ml/min)				p Value
	≥70 (n = 39)	50–69 (n = 41)	<50 (n = 37)	ESRD (n = 25)	
Age (yrs)	63 ± 11	65 ± 11	65 ± 12	65 ± 11	0.7
Women	20 (51%)	18 (44%)	17 (46%)	11 (44%)	0.9
White	24 (62%)	30 (73%)	25 (68%)	16 (64%)	0.8
African-American	2 (5%)	3 (7%)	4 (11%)	8 (32%)	0.006
Unstable angina pectoris	27 (69%)	28 (68%)	30 (81%)	19 (76%)	0.5
Previous myocardial infarction	18 (46%)	28 (68%)	21 (57%)	11 (44%)	0.2
Previous coronary angioplasty	19 (49%)	17 (41%)	12 (32%)	9 (36%)	0.5
Diabetes mellitus	15 (39%)	21 (51%)	17 (46%)	14 (56%)	0.5
Insulin-treated	8 (21%)	11 (27%)	11 (30%)	9 (36%)	0.6
Oral treatment	7 (18%)	21 (51%)	17 (46%)	14 (56%)	0.5
Hypercholesterolemia*	22 (56%)	28 (68%)	21 (57%)	14 (56%)	0.6
Hypertension	23 (59%)	25 (61%)	31 (84%)	23 (92%)	0.005
Smoker	18 (46%)	18 (44%)	20 (54%)	10 (40%)	0.7
Baseline creatinine (mg/dl)	0.87 ± 0.16	1.16 ± 0.34	2.02 ± 1.22	6.0 ± 3.0	<0.001
Ejection fraction	51 ± 7	48 ± 113	47 ± 13	48 ± 14	0.6

\* Hypercholesterolemia was identified if a patient was receiving active medical treatment for high cholesterol or had a total cholesterol >200 mg/dl.

adjustment ( $\text{CrCl}_{\text{female}} = \text{CrCl} \times 0.85$ ). Baseline, procedural, and outcome data on all patients undergoing percutaneous coronary intervention at our institution are recorded on dedicated case report forms and entered into a computerized registry.

**IVUS imaging and analysis:** All IVUS studies were performed before intervention and after intracoronary administration of 200  $\mu\text{g}$  of nitroglycerin. Studies were performed using a commercially available system (Boston Scientific Corporation/SCIMED, Minneapolis, Minnesota). The IVUS catheter was advanced approximately 10 mm distal to the lesion, and the images were recorded during automatic pullback to the aorto-ostial junction at 0.5 mm/s onto 0.5-in high-resolution s-VHS tape for off-line analysis. Qualitative and quantitative analyses were performed according to the American College of Cardiology Task Force on Clinical Expert Consensus on IVUS document.<sup>16</sup>

Cross-sectional measurements were performed using computerized planimetry software (TapeMeasure, INDEC Systems, Mountain View, California). Three sites were measured: proximal and distal reference (sections with the largest lumen and the least plaque within 5 mm proximal and distal to the lesion, which were then averaged) and the site of the minimum lumen cross-sectional area (CSA). The following measurements were obtained. The lumen CSA was defined as the area bounded by the luminal border. The external elastic membrane (EEM) CSA corresponded to the interface between the media and adventitia. The plaque and media CSA was defined as the EEM minus the lumen CSA. Plaque burden was calculated as plaque and media divided by the EEM CSA. The remodeling index was the lesion divided by the mean reference EEM CSA. Calcium deposits were described qualitatively according to their distribution: (1) superficial calcium, when the leading edge of the acoustic shadowing appeared within the shallowest 50% of the plaque,

and (2) deep calcium, when the leading edge of the acoustic shadowing appeared within the deepest 50% of the plaque plus media thickness. The arc of calcium was measured in degrees with an electronic protractor centered on the lumen.

In a subset of patients with optimal images throughout the arterial segment (n = 110), in-depth volumetric 3-dimensional IVUS volumetric analysis was performed every 1 mm, including the EEM, lumen, plaque, plaque burden, arc of calcium, and surface area of calcium. These results were normalized for the measured segment length. This analysis was performed in a subgroup that met the analysis criteria, which included optimal pullback throughout the lesion and the reference segment without interruption or artifacts and with adequate images. If >2 mm of arterial length had suboptimal images, the arterial segment was not used for the volumetric analysis.

**Statistical analysis:** The statistical analysis was performed using either Statistical Analysis Systems or Stat-View software (both SAS Institute, Cary, North Carolina). Data are presented as means ± SDs. Comparisons among the 4 groups were performed by analysis of variance for independent samples and the chi-square test for comparison of categorical values. Post hoc comparisons among groups were performed using Fisher's protected least-significant difference test. Stepwise regression analysis for predictors of volumetric calcium was performed. Age, hypertension, diabetes, and race were included in the model. A p value <0.05 was considered significant.

## Results

The baseline clinical characteristics of all patients are listed in Table 1. More African-American (p = 0.002) and hypertensive (p = 0.002) patients were in the ESRD group. All 4

Table 2  
Intravascular ultrasound analysis

Variable	CrCl (ml/min)				p Value
	≥70 (n = 39)	50–69 (n = 41)	<50 (n = 37)	ESRD (n = 25)	
Coronary artery					
Left main	0 (0%)	1 (2%)	1 (3%)	1 (4%)	0.7
Left anterior descending	16 (41%)	17 (41%)	16 (43%)	13 (52%)	0.8
Left circumflex	10 (26%)	7 (17%)	6 (16%)	5 (20%)	0.7
Right	13 (33%)	16 (39%)	14 (38%)	6 (24%)	0.6
Reference					
EEM CSA (mm <sup>2</sup> )	13.4 ± 4.7	13.3 ± 4.3	12.8 ± 3.8	16.7 ± 7.8	0.0204
Lumen CSA (mm <sup>2</sup> )	8.6 ± 3.5	8.3 ± 2.7	7.9 ± 2.1	11.4 ± 5.8	0.0011
P&M CSA (mm <sup>2</sup> )	4.8 ± 2.1	5.0 ± 2.2	4.9 ± 2.2	5.2 ± 2.3	0.9
Plaque burden (%)	36 ± 10	37 ± 9	38 ± 9	32 ± 7	0.11
Lesion					
EEM CSA (mm <sup>2</sup> )	12.7 ± 4.2	13.2 ± 4.1	11.8 ± 3.9	16.4 ± 6.9	0.0019
Lumen CSA (mm <sup>2</sup> )	2.4 ± 1.1	2.4 ± 1.3	2.2 ± 0.7	3.2 ± 1.7	0.014
P&M CSA (mm <sup>2</sup> )	10.3 ± 3.4	10.8 ± 4.0	9.61 ± 3.8	13.3 ± 5.8	0.0104
Superficial calcium	10 (26%)	11 (27%)	10 (27%)	5 (20%)	0.34
Deep calcium	14 (36%)	12 (30%)	6 (16%)	4 (16%)	0.4
Arc of calcium (°)	164 ± 84	179 ± 99	189 ± 118	243 ± 107	0.0275
Remodeling index	1.0 ± 0.29	1.0 ± 0.26	0.94 ± 0.24	1.07 ± 0.39	0.4

P&M = plaque and media.

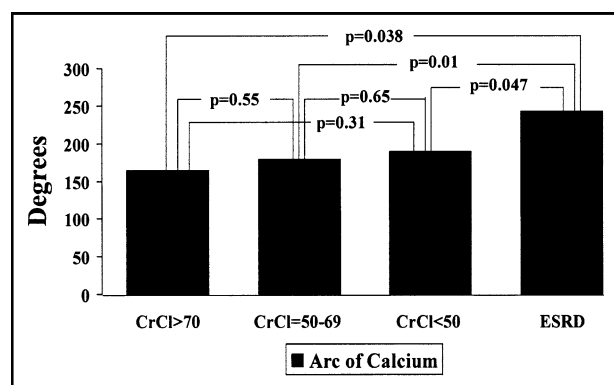


Figure 1. Degrees of arc of calcium according to CrCl.

groups had similar angiographic characteristics. Most lesions (>90%) were located in the proximal or mid-portion of the coronary arteries in all 4 groups. More than 1/2 of all patients (64%) with normal renal function (CrCl ≥70 ml/min) had type A lesions according to the American College of Cardiology/American Heart Association Task Force Classification,<sup>17</sup> and 75% of patients with ESRD had complex lesions classified as type B and/or C (p = 0.06). The results of the IVUS analysis are listed in Table 2 and shown in Figure 1.

No significant difference was found in any of the reference or lesion site IVUS measurements among the 3 groups of patients with CrCl >70, 50 to 69, and <50 ml/min (p = NS for all post hoc comparisons). Conversely, compared with these 3 groups, patients with ESRD had larger reference segment EEM and lumen CSAs; larger lesion site EEM, lumen, and plaque and media CSAs; and larger arcs of calcium (p <0.05 for all post hoc comparisons between patients with ESRD and those with CrCl >70 ml/min, 50 to

69, and <50 ml/min). Calcium location and lesion remodeling were similar in all groups. Area stenosis, calculated by comparing the lesion lumen CSA with the mean reference lumen CSA, measured 70 ± 16%, 70 ± 14%, 71 ± 12%, and 70 ± 14%, respectively.

Similar results were obtained in the volumetric assessment. Patients with mild to moderate renal insufficiency had similar coronary morphometry, but patients with ESRD had larger mean EEMs, increased plaque burden, and increased arterial calcification (Table 3).

To control for the increased prevalence of hypertension in the dialysis group, an age-, gender-, and diabetes-controlled group of hypertensive patients not on dialysis (n = 20) was compared with the hypertensive patients on dialysis (n = 21). The plaque calcification surface (3.6 ± 1.7 vs 6.1 ± 3.6 mm<sup>2</sup>, p = 0.008) and plaque burden (45.3 ± 9.6% vs 53.2 ± 9.0%, p = 0.01) were larger in the patients on dialysis compared with the hypertensive patients not on dialysis.

After performing stepwise regression analysis (including age, hypertension, diabetes, and race in the model), the only predictor for arterial calcification was the creatinine group. All groups had significantly less calcium than the dialysis group (p = 0.0001 for CrCl >70 ml/min, p = 0.013 for CrCl 50 to 69 ml/min, and p = 0.0023 for CrCl <50 ml/min).

## Discussion

The results of the present IVUS study suggest that patients with CRI with known coronary atherosclerosis who are not undergoing dialysis replacement therapy have similar qual-

Table 3  
Volumetric intravascular ultrasound analysis

Variable	CrCl (ml/min)				p Value
	>70 (n = 31)	50–69 (n = 30)	<50 (n = 26)	ESRD (n = 23)	
Mean EEM (mm <sup>2</sup> )	14.40	14.59	13.85	18.32	0.003
Mean lumen (mm <sup>2</sup> )	7.80	7.33	7.53	9.0	NS
Mean plaque (mm <sup>2</sup> )	6.58	7.25	6.37	9.66	<0.001
Mean plaque burden (%)	46	49	45	53	0.01
Mean calcium arc (°)	87°	109°	102°	128°	0.028
Mean calcium surface (mm <sup>2</sup> )	3.54	4.53	4.15	6.3	0.001

itative and quantitative native artery lesion characteristics as patients with normal renal function. IVUS revealed similar quantitative planar and volumetric lesion site and reference segment measurements and qualitative plaque characteristics in predialysis patients with CRI, regardless of the baseline serum creatinine level or calculated CrCl. The transition to ESRD and consequent dialysis replacement therapy is associated with more severe fibrocalcific disease, as evidenced by a larger lesion plaque mass and more lesion site calcification, not only at the lesion site, but also in the nonstenotic segments. Whether the duration of time with ESRD and/or the etiology of CRI play a role in the atherosclerotic process is unknown, because the amount of time these patients had been on dialysis replacement therapy and the etiology were unknown. In a recent study by Goodman et al,<sup>8</sup> they found a higher prevalence of coronary artery calcification in patients treated for >10 years with dialysis replacement therapy, as assessed by electron-beam computed tomography.

Previous studies have shown that even mild renal insufficiency is an independent predictor of significant coronary artery disease and is associated with subclinical atherosclerosis, vascular dysfunction, brachial artery endothelial dysfunction, and carotid artery intima-media thickening.<sup>18,19</sup> However, we only studied patients with known coronary artery disease referred for coronary intervention; therefore, we were unable to assess the impact of mild or more severe renal insufficiency on the frequency of subclinical atherosclerosis.

Cardiac and vascular morbidity and mortality are very common in patients with CRI, particularly in patients with ESRD.<sup>20–23</sup> Although most interventional studies have been performed in patients with ESRD on hemodialysis—patients who have a poor outcome regardless of the intervention—milder degrees of renal insufficiency are also associated with higher in-hospital major adverse cardiac event rates and poor long-term survival. Although stenting has improved the short- and long-term outcomes of patients with CRI who undergo percutaneous coronary intervention, it does not alter the adverse effects of renal insufficiency.<sup>21,22</sup>

Previous studies have shown that the presence and extent of coronary artery calcium correlates with the extent and

severity of atherosclerotic disease and is predictive of cardiovascular events in patients with normal renal function.<sup>24–26</sup> Furthermore, a large analysis of 1,442 patients who underwent IVUS imaging of a native coronary artery demonstrated that the coronary calcium correlates with plaque burden and not with the degree of lumen compromise.<sup>27</sup> In another study that assessed the coronary artery morphology from 27 autopsies in patients with ESRD, increased media thickness and marked calcium were found compared with patients with normal renal function.<sup>28</sup> The pathophysiologic basis for the increased coronary artery disease and coronary artery calcium in patients with ESRD is uncertain. It is important to note that patients on dialysis receive large amounts of calcium in their meals and as calcium salt supplements to control hyperphosphatemia and to prevent secondary hyperparathyroidism. Furthermore, these patients receive substantial amounts of calcium in the dialysate.<sup>8,9</sup> Vascular calcific deposits may also be a consequence of such treatment because the bone of these patients is often unable to handle a large load of calcium and renal excretion is unavailable.

The present study was a retrospective analysis; therefore, the results and conclusions are subject to the limitations inherent in all such reports. The duration of treatment with dialysis was not captured in the present analysis. However, previous reports have shown a direct relation between the duration of dialysis and the extent of coronary artery calcification. The serum creatinine level for the calculation of CrCl is a less precise measure of renal function than the CrCl obtained from a 24-hour urine collection. The relatively small number of patients in the ESRD group may have led to a type II statistical error.

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