Coronary flow reserve is predictive of the risk of cardiovascular death regardless of chronic kidney disease stage

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Microvascular rarefaction is found in experimental uremia, but data from patients with chronic kidney disease (CKD) are limited. We therefore quantified absolute myocardial blood flow and coronary flow reserve (the ratio of peak to resting flow) from myocardial perfusion positron emission tomography scans at a single institution. Individuals were classified into standard CKD categories based on the estimated glomerular filtration rate. Associations of coronary flow reserve with CKD stage and cardiovascular mortality were analyzed in models adjusted for cardiovascular risk factors. The coronary flow reserve was significantly associated with CKD stage, declining in early CKD, but it did not differ significantly among individuals with stage 4, 5, and dialysis-dependent CKD. Flow reserve with preserved kidney function was 2.01, 2.06 in stage 1 CKD, 1.91 in stage 2, 1.68 in stage 3, 1.54 in stage 4, 1.66 in stage 5, and 1.55 in dialysis-dependent CKD. Coronary flow reserve was significantly associated with cardiovascular mortality in adjusted models (hazard ratio 0.76, 95% confidence interval: 0.63-0.92 per tertile of coronary flow reserve) without evidence of effect modification by CKD. Thus, coronary flow reserve is strongly associated with cardiovascular risk regardless of CKD severity and is low in early stage CKD without further decrement in stage 5 or dialysis-dependent CKD. This suggests that CKD physiology rather than the effects of dialysis is the primary driver of microvascular disease. Our findings highlight the potential contribution of microvascular dysfunction to cardiovascular risk in CKD and the need to define mechanisms linking low coronary flow reserve to mortality.

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Cardiovascular disease (CVD) is highly prevalent in patients who have chronic kidney disease (CKD).[1–3] Although the incidence of most CVD manifestations increases as glomerular filtration rate (GFR) declines, associations of CKD with sudden death from CV causes are particularly striking,[1,2,4] and sudden death, not myocardial infarction, actually accounts for most deaths in patients in the most-advanced stages of CKD.

The exaggerated risk of sudden death compared with myocardial infarction in CKD suggests that non-atherosclerotic manifestations of CKD, including rarefaction of the myocardial microvasculature and/or microvascular dysfunction, may induce relative or absolute myocardial hypoxia in the absence of obstructive epicardial atherosclerosis or coronary thrombosis and may lower the threshold for arrhythmia propagation. Experimental studies have consistently demonstrated that ischemia-driven angiogenesis and myocardial capillary supply is reduced in uremic animals,[5,6] and results from several small studies utilizing postmortem samples are consistent with a reduction in left ventricular capillary supply in moderate CKD and end-stage renal disease.[7,8]

Although these data suggest that the myocardial microvasculature may contribute to the increased risk of death from CV causes in CKD, characterizing the relationship between CKD and the myocardial microvasculature more broadly has been hampered by the impracticability of obtaining myocardial tissue from large numbers of individuals with and without CKD. However, microvascular function can be non-invasively assessed by measuring coronary flow reserve (CFR)—the ratio of peak to basal myocardial blood flow—using positron emission tomography (PET). We and others have shown that CFR is strongly and independently associated with death from CV causes, in a wide range of patient populations, and improves risk stratification, even after accounting for the presence of obstructive atherosclerosis.[9–11] Similar associations between CV events and CFR are present in the setting of CKD, and CFR appears to be a strong predictor of CV risk in both moderate CKD and dialysis-dependent CKD.[12,13] We have demonstrated that mildly reduced kidney function is associated with accelerated decline

in CFR over time, in a small study of individuals without diabetes.[14] Although these studies suggest that low CFR and microvascular dysfunction may play a role in the pathogenesis of uremic CVD, the broader association of kidney function with CFR remains poorly characterized.

Our objective in this study was to characterize myocardial microvascular function by analyzing the association between kidney function and CFR across the full spectrum of CKD. We hypothesized that CFR would be reduced in CKD and that low CFR would be associated with worse CV outcomes in CKD.

RESULTS
Baseline characteristics

In all, 3946 individuals underwent myocardial perfusion PET scanning during the study period and had sufficient information for calculation of estimated GFR (eGFR). A total of 198 (5.6%) individuals had preserved kidney function, 602 (17.2%) had stage 1 CKD, 1292 (37.0%) had stage 2 CKD, 901 (25.8%) had stage 3 CKD, 216 (6.2%) had stage 4 CKD, 112 (3.2%) had non–dialysis-dependent stage 5 CKD, and 175 (5.0%) had stage 5 CKD and were on dialysis (Table 1). Baseline characteristics differed by CKD stage. In general, increasing severity of CKD was associated with increasing comorbidity, including older age, hypertension, diabetes, prior myocardial infarction, heart failure, and prior revascularization (Table 1).

Aside from serum creatinine and calcium, which were universally available, other laboratory parameters were often missing (Table 2). Among individuals with available values, those with more severe CKD had lower low-density lipoprotein cholesterol and hemoglobin concentrations and higher parathyroid hormone and phosphorous concentrations.

Table 1 | Baseline characteristics according to CKD stage

Characteristic	Preserved kidney function (n = 198)	Stage 1 CKD (n = 602)	Stage 2 CKD (n = 1292)	Stage 3 CKD (n = 901)	Stage 4 CKD (n = 216)	Stage 5 CKD (n = 112)	Dialysis (n = 175)	*P* value
Demographics								
Age, yr	49.5 ± 9.8	58.5 ± 10.2	69.7 ± 14.0	77.7 ± 13.7	78.6 ± 15.8	69.7 ± 17.8	64.4 ± 19.8	<0.001
Male	67 (33.8)	275 (45.7)	651 (50.4)	473 (52.5)	123 (56.9)	63 (56.3)	96 (57.5)	<0.001
Race								<0.001
Black	71 (35.9)	121 (20.1)	184 (14.2)	117 (13.0)	35 (16.2)	27 (24.1)	72 (43.4)	
White	38 (19.2)	374 (62.1)	961 (74.4)	709 (78.7)	169 (78.2)	68 (60.7)	69 (41.6)	
Other	89 (44.9)	107 (17.8)	147 (11.4)	75 (8.3)	12 (5.6)	17 (15.2)	25 (15.1)	
Medical history								
Hypertension	136 (68.7)	444 (73.8)	1050 (81.3)	818 (90.8)	200 (92.6)	105 (93.8)	155 (88.6)	<0.001
Diabetes	57 (28.8)	165 (27.4)	354 (27.4)	331 (36.7)	105 (48.6)	51 (45.5)	88 (50.3)	<0.001
Myocardial infarction	31 (15.7)	140 (23.3)	351 (27.2)	313 (34.7)	90 (41.7)	28 (25.0)	50 (28.6)	<0.001
Heart failure	5 (2.5)	16 (2.7)	69 (5.3)	83 (9.2)	34 (15.7)	8 (7.1)	15 (8.6)	<0.001
PVD	5 (2.5)	18 (3.0)	72 (5.6)	87 (9.7)	22 (10.2)	4 (3.6)	25 (14.3)	<0.001
COPD	27 (13.6)	57 (9.5)	141 (10.9)	109 (12.1)	26 (12.0)	8 (7.1)	14 (8.0)	0.27
Hyperlipidemia	90 (45.5)	393 (65.3)	891 (69.0)	682 (75.7)	149 (69.0)	78 (69.6)	101 (57.7)	0.003
Prior CABG	4 (2.0)	44 (7.3)	177 (13.7)	178 (19.8)	50 (23.1)	15 (13.4)	19 (10.9)	<0.001
Prior PCI	17 (8.6)	127 (21.1)	292 (22.6)	244 (27.1)	50 (23.1)	14 (12.5)	33 (18.9)	<0.001
Physical examination								
Rest HR, bpm	73.8 ± 14.1	71.3 ± 13.1	69.9 ± 12.9	70.3 ± 12.9	71.1 ± 12.4	73.2 ± 13.3	79.4 ± 60.5	<0.001
Rest SBP, mm Hg	141.1 ± 26.3	142.2 ± 24.2	145.4 ± 25.3	145.9 ± 26.8	147.1 ± 28.2	157.1 ± 26.2	151.4 ± 31.2	<0.001
Rest DBP, mm Hg	74.4 ± 13.4	73.4 ± 12.1	72.8 ± 12.4	71.4 ± 13.4	71.9 ± 14.2	77.0 ± 15.1	74.8 ± 14.7	<0.001
BMI, kg/m²	33.1 ± 10.0	31.6 ± 8.46	30.2 ± 7.5	29.8 ± 7.3	29.1 ± 7.1	29.1 ± 6.7	27.7 ± 6.5	<0.001
Medications								
ACE or ARB	60 (30.3)	212 (35.2)	540 (41.8)	388 (43.1)	54 (25.0)	39 (34.8)	62 (35.4)	<0.001
Aspirin	95 (48.0)	358 (59.5)	854 (66.1)	610 (67.7)	148 (68.5)	55 (49.1)	95 (54.3)	<0.001
Beta blockers	89 (44.9)	333 (55.3)	809 (62.6)	658 (73.1)	163 (75.5)	81 (72.3)	127 (72.6)	<0.001
Calcium channel blocker	26 (13.1)	100 (16.6)	291 (22.5)	258 (28.6)	76 (35.2)	50 (44.6)	68 (38.9)	<0.001
Lipid-lowering	80 (40.4)	337 (56.0)	826 (63.9)	658 (73.0)	157 (72.7)	72 (64.3)	110 (62.9)	<0.001
Digoxin	2 (1.0)	13 (2.2)	47 (3.6)	61 (6.8)	7 (3.2)	1 (0.9)	1 (0.6)	<0.001
Insulin	24 (12.1)	78 (13.0)	178 (13.8)	175 (19.4)	63 (29.2)	35 (31.3)	55 (31.4)	<0.001
Oral hypoglycemics	29 (14.6)	74 (12.3)	142 (11.0)	98 (10.9)	15 (6.9)	5 (4.5)	6 (3.4)	0.001
Nitrates	18 (9.1)	67 (11.1)	160 (12.4)	163 (18.1)	51 (23.6)	18 (16.1)	18 (10.3)	<0.001

Baseline characteristics of the study population. Values are n (%) or mean ± SD. Categorical *P* values using analysis of variance for continuous variables, and χ^2 tests for categorical values.
ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; bpm, beats per minute; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HR, heart rate; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SBP, systolic blood pressure.