CKD and Coronary Collateral Supply in Individuals Undergoing Coronary Angiography after Myocardial Infarction

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Summary

Background and objectives CKD patients have high mortality risk after myocardial infarction (MI). An adequate supply of coronary collaterals to the culprit vessel responsible for MI is associated with reduced risks of death and complications. Whether a diminished supply of collaterals contributes to the high risk in CKD patients is uncertain.

Design, setting, participants, & measurements Quantitative coronary angiography was performed in a consecutive series of individuals with (n=58) and without (n=165) CKD (estimated GFR <60 ml/min per 1.73 m^2) who underwent coronary angiography at the time of MI. Collateral supply was analyzed and candidate predictors were assessed in patient-level and individual artery-level models using logistic regression and ordered categorical regression, respectively.

Results There were no significant differences in collateral supply among 58 CKD patients and 165 individuals with preserved renal function. Culprit artery collaterals were present in 25.0% of CKD patients compared with 27.2% of individuals with preserved renal function (P=0.76). The odds of having an adequate supply of culprit vessel collaterals were also not significantly different in individuals with and without CKD, respectively. CKD patients were 2.22-fold more likely to have visible collaterals to the nonculprit vessels in unadjusted analyses. The difference was not significant after correction for percent stenosis and comorbid factors.

Conclusions Our results do not support an independent association between CKD and diminished collateral supply to either the culprit or nonculprit vessels in MI. Additional studies are warranted to better define associations between myocardial capillary supply, collateral supply, and the full range of human CKD.
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Introduction

CKD is increasingly recognized as a cardiovascular risk factor (1–4). Although the risk of myocardial infarction (MI) increases as GFR declines (5), the increased risk of adverse events after MI is even more striking and is not fully explained by the increased age or comorbidity of individuals with CKD (6–9). Individuals with CKD present with higher Killip class (6), and are significantly more likely to develop shock or congestive heart failure or to die within 30 days of an MI (7,8) than those with preserved renal function. Long-term complications are similarly increased, and the risks of recurrent MI and cardiovascular death rise severalfold as the severity of renal impairment increases (9).

Why outcomes of MI are worse in individuals with CKD is uncertain, but a potential clue comes from studies demonstrating that a well developed coronary collateral circulation can reduce myocardial damage, preserve myocardial function, and improve clinical outcomes of coronary artery obstruction (10–14). These observations suggest that a reduced supply of collaterals could be an important factor in the increased severity of MI in CKD. Experimental studies

show that infarct size is increased in the presence of renal failure (15) and that uremia is characterized by inhibition of ischemia-induced angiogenesis (16) and rarefaction of myocardial microvessels (17), further supporting the concept that defects in coronary collateralization may play an important part in the association of CKD and cardiovascular disease.

Whether these processes lead to a diminished supply of coronary collaterals in human CKD is unknown. A differential supply of collaterals to the infarct-related artery could play a critical role in the differential outcomes of MI in individuals with and without CKD and might be a modifiable therapeutic target. To better understand the role of collaterals in the association of CKD with cardiovascular outcomes, we assessed collateral supply in individuals undergoing coronary angiography after admission for MI.

Materials and Methods
Study Population

We analyzed consecutive patients at Brigham and Women's Hospital who were admitted with an ST

elevation myocardial infarction (STEMI) between January 2001 and September 2002 or a non-ST elevation MI (NSTEMI) between January 2002 and February 2003 and underwent coronary angiography before discharge. Exclusion criteria included history of coronary artery bypass grafting, cardiac transplant, angioplasty within the previous 30 days, inability to identify the culprit lesion, inadequate angiographic views for assessment of collaterals, or absence of sufficient data to assess renal function. The STEMI and NSTEMI cohorts were otherwise assessed identically. The final cohort of 223 patients represented 27% of the 824 individuals who presented with STEMI or NSTEMI during the study period.

Clinical Variables

Medical records were reviewed for demographics, laboratory results, and comorbidities. MI was defined as either STEMI (chest pain with ST elevation in two contiguous electrocardiographic leads) or NSTEMI (ischemic symptoms with elevated cardiac biomarkers or ischemic electrocardiographic changes not meeting the criteria for STEMI). Creatinine and other laboratory results at the time of angiography were recorded. Estimated GFR (eGFR) was calculated using a single preprocedure creatinine and the abbreviated Modification of Diet in Renal Disease (MDRD) equation (18). CKD was defined as an eGFR <60 ml/min per 1.73 m² (19). Measures of urinary protein excretion were not collected.

Angiographic Analyses

Coronary angiograms were analyzed by a single reader using quantitative coronary angiographic software (version 5.1; Cardiology Medis System, Nuenen, The Netherlands), with blinding to renal function. After calibration against catheter dimensions (20), using standardized angiographic projections to minimize foreshortening and measurement variability (21), the maximal percent diameter stenosis was measured in the left main and each of the three epicardial coronary arteries. Stenosis was recorded only when it was $\geq20\%$, the lower limit of reliable discrimination. Arteries with diameters <1.75 mm were not assessed because these segments were considered too small for accurate QCA.

Culprit lesions responsible for MI were identified as the site of maximal stenosis or occlusion in conjunction with clinical and electrocardiographic findings. Prior coronary interventions and percutaneous interventions performed during the index procedure were recorded.

Collaterals were scored using the Rentrop classification (22), a four-point, semiquantitative scoring system including the following grades: 0, no visible collaterals; 1, filling of side branches of the artery via collateral channels; 2, partial filling of the epicardial portion of the artery via collaterals; and 3, complete filling of the epicardial segment via dilated collaterals. Collaterals were considered present with scores ≥1 and were considered adequate with scores ≥2.

Statistical Analyses

Variables are reported as mean $\pm$ SD, median, and interquartile range (IQR) or counts (%). We used t tests and Mann–Whitney tests to compare normally and non-normally distributed continuous variables, respectively. The chi-squared test was used for categorical variables. In the primary analysis, the associations between CKD and other baseline characteristics and binary measures of culprit vessel collateral supply were assessed using univariate and multivariate logistic regression models. Ordered categorical regression models were used for secondary analyses with the Rentrop score in the culprit vessel as the outcome variable.

Collateral supply in nonculprit vessels was assessed at the level of the individual patient and used the individual artery as the unit of analysis. In these analyses, collateral supply was defined both in a binary fashion (any collaterals, adequate collaterals) for the primary analysis and on the basis of the Rentrop score within the artery for secondary analyses. Because vessel-level analyses included ≥1 artery per individual, robust SEMs correcting for potential intra-individual correlation between arteries from a single individual were used (23).

Because the number of outcomes constrained the number of factors incorporated into models and univariate associations were mostly nonsignificant, covariates were chosen on the basis of known or presumed biologic or clinical association with collateral supply. Variables for hyperlipidemia and degree of baseline stenosis were added to the base models where feasible. Model fit and assumptions were checked for each model. Analyses were performed using Stata software (version 9.2; Stata Corporation, College Station, TX). P values <0.05 were considered significant.

Human Participants

This project was approved by the Brigham and Women's Hospital institutional review board.

Results

Baseline Characteristics

The study cohort included 58 patients with stage ≥3 CKD and 165 individuals without significant renal impairment (Table 1). Although only two patients had ESRD, the mean eGFR was significantly lower among individuals with CKD (42.9 ± 14.3) than in those with preserved renal function (87.7 ± 20.6). Individuals with CKD were also older (71.4 ± 11.7 versus 61.6 ± 11.8 years; $P<0.001$), less likely to be male (44.8% versus 71.5%; $P<0.001$), and more likely to have diabetes (41.4% versus 21.8%; $P=0.01$), hypertension (89.7% versus 71.5%; $P=0.004$), or a previous MI (32.8% versus 15.2%; $P=0.01$) than individuals with preserved renal function. Overall, 58 patients had visible collaterals to the infarct-related artery (25% in patients with CKD and 27.2% in patients with preserved renal function; $P=0.76$).

Univariate Associations with Collateral Supply to the Infarct Artery

There was no significant association between baseline renal function and the presence of collaterals to the infarct artery (Table 2). CKD was present in 26.3% of individuals without any collaterals to the infarct vessel and in 24.1% of individuals with angiographic collaterals (odds ratio [OR], 0.89; 95% confidence interval [95% CI], 0.44–1.79; $P=0.75$). Among other factors examined, only an infarct location within the right coronary artery (OR, 4.22; 95% CI, 1.81–9.86; $P=0.001$) was significantly associated with the collateral supply to the infarct artery. The presence of CKD was

Table 1.   Baseline characteristics of the study population

Characteristic	CKD (*n*=58)	Normal Kidney Function (*n*=165)	*P* Value
Demographics			
age (yr)	71.4±11.7	61.6±11.8	<0.001
male sex	26 (44.8)	118 (71.5)	<0.001
race	–	–	0.84
white	49 (84.4)	135 (81.8)	–
black	5 (8.6)	16 (9.7)	–
other	4 (6.9)	14 (8.5)	–
Medical history			
diabetes	24 (41.4)	36 (21.8)	0.01
hyperlipidemia	42 (72.4)	97 (58.8)	0.08
hypertension	52 (89.7)	118 (71.5)	0.004
present smoking	4 (6.9)	47 (28.5)	<0.001
past smoking	16 (27.6)	41 (24.8)	0.73
prior myocardial infarction	19 (32.8)	25 (15.2)	0.01
family history of coronary artery disease	14 (24.1)	57 (34.5)	0.19
ESRD	2 (3.8)	0 (0.0)	0.06
Laboratory data			
creatinine (mg/dl)	2.0±1.9	0.9±0.2	<0.001
estimated GFR (ml/min per 1.73 m^2)	42.9±14.3	87.7±20.6	<0.001
ejection fraction (%)	46.7±12.0	47.5±12.3	0.70
peak creatine kinase (IU/L)	380 (120–873)	331 (116–788)	0.82
Angiographic stenosis (%)			
culprit vessel	76.5±0.20	75.8±0.20	0.83
nonculprit vessel	53.8±0.21	44.7±21.4	<0.001
Infarct characteristics			
ST elevation myocardial infarction	7 (12.1)	46 (27.9)	0.02
infarct location	–	–	0.46
left main	4 (6.9)	4 (2.5)	–
left anterior descending artery	18 (31.0)	46 (27.8)	–
left circumflex artery	18 (31.0)	57 (34.5)	–
right coronary artery	16 (27.6)	55 (33.3)	–
ramus	2 (3.4)	3 (1.9)	–
Congestive heart failure on presentation	5 (15.2)	15 (16.1)	1.00

Data are presented as *n* (%), mean ± SD, or median (interquartile range).

similarly unrelated to whether collateral supply to the infarct artery was adequate. Ejection fraction was higher among patients without collaterals to the infarct vessel (48.5%±11.8%) than among those with collaterals (43.3%± 11.9%; *P*=0.01), suggesting more significant underlying coronary disease in those with developed collaterals.

Univariate Associations with Nonculprit Collateral Supply

Although CKD was not associated with collateral supply to infarct vessels, collateral supply to nonculprit arteries was increased in CKD patients. Individuals with CKD were 2.22-fold more likely to have visible collaterals (95% CI, 1.02–4.84; *P*=0.05) to nonculprit vessels and were also more likely to have an adequate supply of collaterals in the nonculprit vessels (OR, 2.43; 95% CI, 1.07–5.51; *P*=0.03). Because greater degrees of chronic vascular stenosis would be expected to provide an increased stimulus for collateral formation, we examined the association between CKD and collateral formation stratified by the maximal percent stenosis within individual nonculprit vessels. This diminished association with CKD, but trends toward an increased supply of collaterals remained apparent at every level of stenosis (Figure 1). As shown in Figure 2,

the total collateral supply of the heart was not significantly different in individuals with and without CKD. Although collateral supply seemed to be moderately increased in the small number of individuals with stage 4–5 CKD, this difference was largely abolished after correction for the number of vessels with ≥50% diameter stenosis.

Adjusted Analyses

Multivariable analyses correcting for potential confounding variables such as age, diabetes, smoking, infarct location, or percent diameter stenosis were performed using both patient-level and vessel-level units of analysis (Table 3). Although the majority of these analyses yielded point estimates compatible with an increased supply of collaterals in individuals with CKD compared with those without CKD, the CIs were broad. None of the estimates were suggestive of a significant or borderline significant association between CKD and collateral supply.

Discussion

In this study, we hypothesized that a reduced supply of collaterals to the culprit artery responsible for MI could be

Table 2.   Unadjusted associations with presence of any collaterals or adequate collaterals to the infarct artery

Characteristic	Any Collaterals			Adequate Collaterals		
	Odds Ratio	95% Confidence Interval	P Value	Odds Ratio	95% Confidence Interval	P Value
Demographics						
age (yr)						
≤40	1.00	Ref	Ref	1.00	Ref	Ref
41–60	0.25	0.02–2.92	0.27	0.20	0.17–2.25	0.19
61–80	0.11	0.01–1.25	0.08	0.08	0.01–0.96	0.05
≥80	0.29	0.02–3.83	0.35	0.18	0.13–2.43	0.20
male sex	1.45	0.76–2.78	0.27	2.06	0.98–4.32	0.06
race						
white	1.00	Ref	Ref	1.00	Ref	Ref
black	1.00	0.30–3.35	0.99	0.92	0.24–3.45	0.90
other	0.47	0.13–1.68	0.25	0.63	0.18–2.27	0.48
Medical history						
diabetes	0.92	0.46–1.82	0.81	0.90	0.43–1.89	0.79
hyperlipidemia	0.91	0.49–1.69	0.77	1.11	0.57–2.17	0.76
hypertension	0.74	0.37–1.46	0.38	0.86	0.41–1.82	0.70
present smoking	1.41	0.71–2.81	0.33	1.38	0.67–2.89	0.39
past smoking	1.14	0.58–2.25	0.70	1.30	0.65–2.67	0.47
prior MI	1.38	0.67–2.83	0.38	1.09	0.49–2.41	0.83
family history of coronary artery disease	1.29	0.68–2.42	0.44	1.26	0.64–2.48	0.50
ESRD	2.76	0.17–44.89	0.48	3.72	0.23–60.7	0.36
CKD	0.89	0.44–1.79	0.75	0.86	0.40–1.82	0.69
Infarct characteristics						
ST elevation myocardial infarction	1.02	0.51–2.06	0.95	0.83	0.38–1.81	0.64
infarct location						
left anterior descending artery	1.00	Ref	Ref	1.00	Ref	Ref
left circumflex artery	1.93	0.80–4.66	0.14	3.46	1.20–9.99	0.02
right coronary artery	4.22	1.81–9.86	0.001	6.03	21.4–17.00	0.001
other	2.04	0.35–11.71	0.43	1.69	0.17–16.58	0.65
Congestive heart failure on presentation	0.88	0.29–2.66	0.82	0.59	0.28–1.26	0.18

The presence of any collaterals was defined as a Rentrop score ≥1. Adequate collaterals were defined as a Rentrop score ≥2.

an important factor underlying the increased risk of death in CKD, and we therefore analyzed collateral supply in individuals undergoing coronary angiography after MI. Contrary to expectations, we did not find a significant decrease in collateral supply to the infarct artery. Instead, there was a nonsignificant trend toward more collateralization of both the culprit vessel and the noninvolved coronary arteries in individuals with CKD that was largely explained by the greater degrees of vascular stenosis in individuals with CKD. The higher frequency of prior MI in patients with CKD may offer an additional explanation for this trend.

Our results suggest that collateral supply is similar in individuals with and without CKD, and that the generation and maintenance of collaterals in either acutely or chronically ischemic arteries is not markedly inhibited as GFR declines. Although we were unable to directly assess the association of collateral supply with post-MI outcomes in this cohort, our findings suggest that collateral supply is unlikely to be a major factor underlying either the high incidence of cardiovascular death in individuals with CKD or the increased risk of post-MI death.

To our knowledge, ours is the first study to report on the association of CKD and collateral supply to the culprit vessel in acute MI. Although collateral supply to the vessel responsible for MI in individuals with and without CKD has not been previously described, Sezer et al. found in a cohort of 268 individuals undergoing coronary angiography that the total collateral score (sum of individual Rentrop scores for all epicardial vessels) was 41% lower (P<0.001) in individuals with creatinine clearance ≤80 ml/min (24). Our results were qualitatively unchanged when we substituted this cutoff (data not shown), and the differential findings are likely related to institutional differences in the threshold for angiography, as well as the use of a summed collateral score without correction for the degree of stenosis, the use of visual estimates for quantitation of stenosis rather than quantitative digital angiography, and the unusual definition of CKD as a creatinine clearance <80 ml/min by Sezer et al. In addition, the majority of patients studied by Sezer et al. presented with stable angina, and no distinction was made between collateral supply to the culprit artery and other vessels. Additionally, multicenter studies including patients with both stable and unstable patterns of coronary disease are
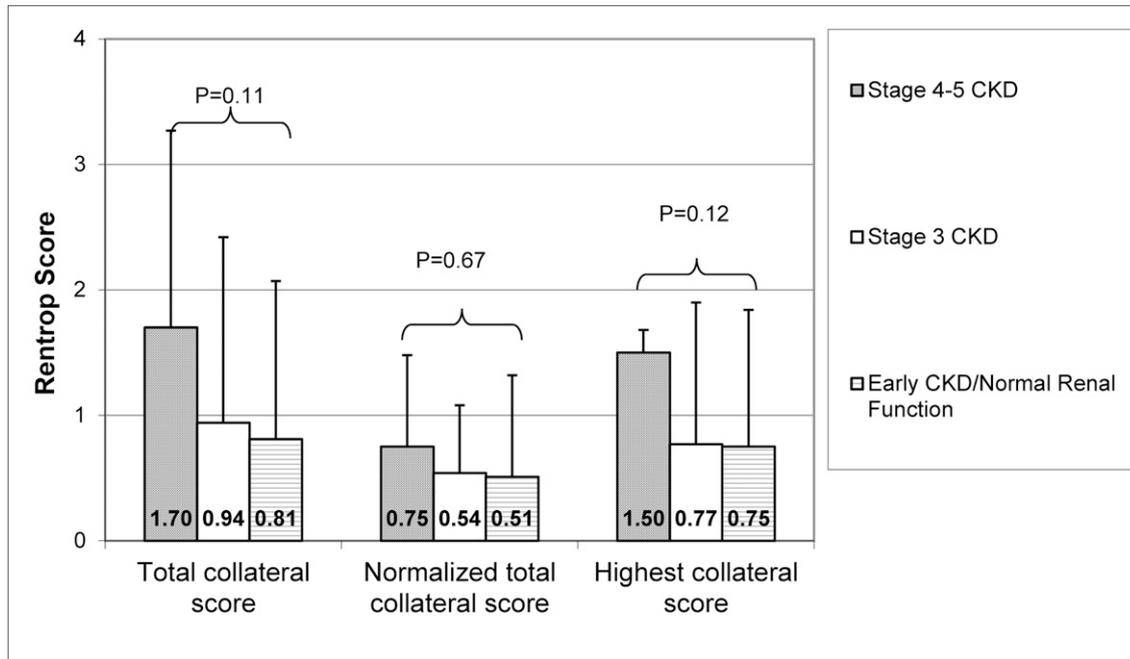
Figure 1. | **Collateral score in nonculprit vessels according to baseline degree of stenosis**.
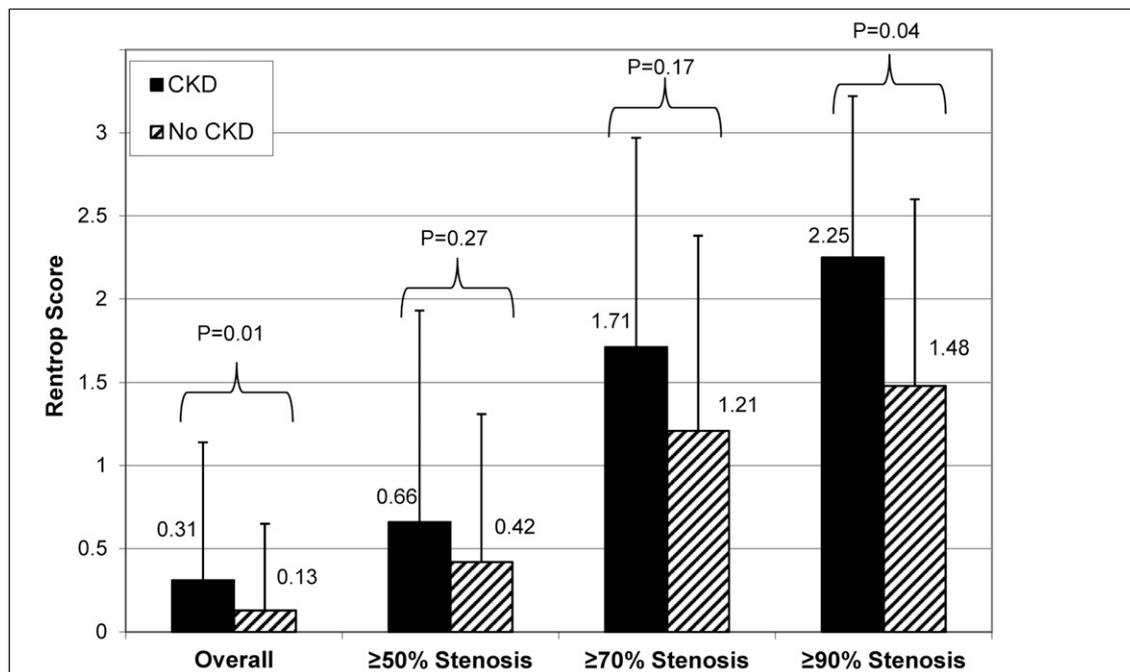

Figure 2. | **Total collateral supply according to baseline renal function**. Total collateral score represents the summed collateral score across all vessels from a given individual. Normalized score represents total score normalized to the number of vessels with ≥50% diameter stenosis. Highest collateral score represents the highest score within any of the epicardial arteries in an individual patient.

needed for further elucidation of the factors affecting collateral supply.

Although our findings conflict with those of Sezer *et al.*, they are consistent with a few prior studies of coronary microvascular circulatory function. Chade *et al.* used coronary flow wires to measure mid left anterior descending

artery coronary flow reserve in patients without significant coronary disease, and found no independent association between CKD and a low flow reserve (25). A similar study by Koivuviita *et al.*, which included 31 individuals (21 with CKD) without cardiovascular disease who underwent myocardial positron emission tomography, also did not

Table 3. Adjusted associations between CKD and collateral supply to culprit and nonculprit vessels

Outcome	Odds Ratio	95% Confidence Interval	P Value
Patient-level analysis (binary measures)			
any collaterals to infarct vessel[a]	1.24	0.55–2.79	0.60
adequate collateral supply to infarct vessel[a]	1.26	0.52–3.05	0.62
any collaterals to noninfarct vessel[b]	1.64	0.61–4.39	0.33
adequate collateral supply to noninfarct vessel[b]	1.56	0.56–4.34	0.39
Vessel analysis			
any collaterals to nonculprit vessels[b]	2.42	(0.74, 7.92)	0.14
adequate collaterals to nonculprit vessels[b]	2.33	(0.70, 7.69)	0.17
collateral score in infarct artery[c]	0.91	(0.40, 2.11)	0.83
collateral score in noninfarct arteries[d]	1.97	(0.71, 5.51)	0.19

Patient-level and vessel-level adjusted analyses of the association between CKD and collateral formation. For patient-level analysis, the individual patient with or without CKD served as the unit of analysis and only one outcome per patient was allowed in the logistic regression models. For vessel-level analyses, the individual vessels served as the unit of analysis in logistic models with the Rentrop score (0–3) serving as the dependent variable in a multivariable ordered logistic regression models. Robust SEMs were used in the vessel analysis of noninfarct collateral score to account for correlations between multiple vessels within an individual patient. All models were adjusted for age, sex, race, diabetes, MI type, hypertension, smoking, and infarct location in addition to the covariates listed below in the footnotes.
[a]None.
[b]Number of diseased vessels.
[c]Hyperlipidemia.
[d]Hyperlipidemia and percent diameter stenosis.

show a significant association between nuclear flow reserve and CKD (26). In the context of these prior investigations, our findings raise new questions about animal models that have consistently demonstrated microvascular dropout in the myocardium of uremic animals (17,27–29).

A possible and important implication of our findings is that microvascular function of the heart is not altered in human CKD. However, changes in aspects of microcirculatory function other than the supply of angiographically visible collaterals—such as increases in aortic and ventricular stiffness with resulting changes in diastolic coronary flow, metabolic changes in the concentration of potassium and uric acid, or decreases in the supply of myocardial capillaries—could be more important contributors to changes in myocardial perfusion and post-MI outcomes in CKD.

Other explanations for the discordance between our clinical findings and experimental data merit consideration. The etiology, duration, and degree of renal dysfunction differ in clinical and experimental studies and could account for the different findings. The duration and nature of the primary underlying stimuli for new vessel formation—atherosclerotic stenosis of the epicardial coronary arteries in humans versus ventricular hypertrophy and myocardial fibrosis in animal models—may also account for the differential results. In addition, the Rentrop score and similar clinical tools are crude and imperfect measures of microvascular supply (22) compared with the pathologic techniques used in animal studies. Finally, the conflicting findings may relate to the biologic distinction between arteriogenesis and the formation of collaterals (measured in human studies) and angiogenesis and capillary homeostasis (the primary processes measured in experimental studies) (30). Careful clinical-pathologic investigations are needed to elucidate how capillary and collateral homeostases are correlated in human CKD and to better define their relationship with renal function.

Strengths of our study include the use of quantitative coronary angiography to assess stenosis, a cohort with uniform indications for coronary angiography, and the analysis of outcomes on a patient and vessel level. Although there are no *a priori* reasons for collateral formation to differ in patients in different centers, the thresholds for coronary angiography, particularly in individuals with and without CKD, may vary at different hospitals. Although the universal presence of acute MI in the patients included in our study may have limited these differences, confirmation of our findings in multicenter studies is desirable.

Our study also excluded patients with prior bypass surgery, no clear culprit lesion, recent coronary intervention, or insufficient angiographic views to perform the requisite analysis, and these criteria may limit the generalizability of the analysis. Additional issues include the use of a single reader for quantitative angiography, as well as the absence of data on vessel diameter or time from symptom onset to angiography.

The drawbacks of the MDRD equation are also well known (18). Direct measurement of outpatient GFR and urinary protein excretion would have been preferable to estimation of GFR using only a single creatinine drawn at the time of hospitalization. Unfortunately, despite the known associations with cardiovascular outcomes (31), protein excretion was not recorded and data on preadmission creatinine were not universally available. Nevertheless, estimating equations are widely used to study the association of CKD with cardiovascular disease. In addition, the mean creatinine in the subgroup with CKD was 2.0 mg/dl. This is consistent with at least moderate CKD, a situation in which the MDRD equation performs relatively well (18) and in which misclassification should be limited.

A related issue is that our study had <80% power to rule out small differences (*e.g.,* changes of ≤10%) in collateral supply that could be important contributors to cardiovascular risk on a population level. Given the small size of the CKD population in this study, a more limited population with advanced CKD, and the markedly unequal distribution of diabetes and hypertension in the groups with and without CKD, our ability to fully adjust for all confounders or to detect changes in patients with more advanced CKD was limited. We cannot rule out the possibility of small decreases in collateral supply as GFR declines, particularly at very low levels of residual renal function. Given the typical prevalence rates of obstructive atherosclerosis and CKD in patients undergoing coronary angiography, studies involving >1000 MI patients may be necessary to provide sufficient numbers of obstructed arteries and advanced CKD patients for more definitive answers. However, a subgroup analysis (Figure 2) was not suggestive of a reduction in collateral supply in those with stage 4–5 CKD, and our point estimates were suggestive of increased, rather than decreased, collateral supply in CKD. Within the limits of our analysis, it thus seems unlikely that we missed a significant inhibitory effect of CKD on coronary collateralization. This study is the first to analyze the association of CKD with collateral supply to the infarct artery; as such, we believe our findings provide potentially important new insights into the association of CKD with cardiovascular disease, despite the limitations. However, confirmatory studies, particularly in stage 4–5 CKD, are clearly warranted.

In conclusion, we analyzed collateral supply to the culprit and nonculprit vessels at the time of MI and found that CKD was not significantly associated with the extent of collateralization to either the culprit or nonculprit vessels. Differences in coronary collateral supply to the culprit infarct vessel may not be an important factor in the association of cardiovascular death with CKD. Additional studies are warranted to better define the associations between myocardial capillary supply, collateral supply, and the full range of human CKD.

Disclosures
None.

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