KI REPORTS
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Clinical Implications of Coronary Microvascular Dysfunction in Patients with CKD

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Kidney Int Rep (2023) **8,** 10–13; https://doi.org/10.1016/j.ekir.2022.11.010

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Coronary microvascular dysfunction (CMD) encompasses the range of structural and functional changes in the coronary microvasculature that cause diminished coronary blood flow and consequently myocardial ischemia.[1] CMD may be the result of impaired vasodilatory capacity or increased coronary microvascular vasoconstriction. Structural impairments accompanying CMD are predominantly characterized by intramural arteriole and capillary luminal narrowing, perivascular fibrosis, and microvascular rarefaction, often associated with left ventricular muscle hypertrophy.[1,2] Coronary flow reserve (CFR) is an integrated measure of flow through both the large epicardial arteries and the coronary microcirculation and can be assessed noninvasively using positron emission tomography, magnetic resonance imaging, or Doppler echocardiography. These noninvasive methods, however, cannot differentiate between impaired CFR because of epicardial stenosis or alterations in the coronary microvasculature.

CFR can also be evaluated in the cardiac catheterization laboratory when performing physiologic testing in a coronary artery. To measure CFR invasively, a temperature sensor-tipped guidewire is placed in the distal portion of the coronary artery and a nonendothelium-dependent vasodilator (most commonly adenosine) is infused to induce hyperemia. CFR is calculated indirectly via thermodilution using saline bolus transit time through the coronary artery and is defined as the ratio of the maximum hyperemic flow velocity to the basal coronary flow velocity. It is well established that impaired CFR is associated with increased risk of major adverse cardiovascular events (MACEs).[3] The Women's Ischemia Syndrome Evaluation study investigated the relationship between MACE and invasively measured CFR in women referred for coronary angiography for the evaluation of suspected ischemia. They found that CFR <2.32 best predicted adverse outcomes in women with ischemia with nonobstructive coronary artery disease over angiographic CAD severity and other risk factors, with a 3-fold higher risk of MACE in those with abnormal CFR compared with those normal CFR.[3]

The thermodilution-based index of microcirculatory resistance (IMR) is a measure to selectively assess the microvascular dilatory capacity. IMR is calculated as the product of the distal coronary pressure and mean transit time of a saline bolus during maximal hyperemia.[1] Abnormal IMR is defined as >25 Units. Abnormal IMR in combination with low CFR has been associated with increased MACE in patients with ischemia with nonobstructive coronary artery.[1] Using these parameters together can further categorize the etiology of CMD, which can help guide therapy and potentially improve patient outcomes. The 2021 American College of Cardiology/American Heart Association Chest Pain Guideline and 2019 European Society of Cardiology Guidlines on Chronic Coronary Syndromes provide a class IIa recommendation for invasive coronary functional testing to improve risk stratification in patients with ischemia with nonobstructive coronary artery.[4,5] If CMD is discovered, intensification of preventative treatments and optimization of symptom guided medical therapies are recommended (class I).[4,5] Some of these therapies include beta blockers; calcium channel blockers; angiotensin-converting enzyme inhibitors; as well as trimetazidine and ranolazine, which work by decreasing myocardial oxygen

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Table 1. Ongoing randomized clinical trials investigating the use of guideline-directed medical therapies for coronary microvascular dysfunction

Trial Title	Location	Trial start date	Interventions	Primary outcome measure	Are CKD patients excluded in this trial?
Women's ischemia trial to reduce events in nonobstructive CAD (WARRIOR)	United States	2018	Aspirin ACEi/ARB Statin[a] Placebo	First occurrence of MACE as death, nonfatal MI, nonfatal stroke/transient ischemic attack or hospitalization for heart failure or angina	Yes. Severe renal impairment (eGFR < 30)
Efficacy of Diltiazem to improve coronary microvascular dysfunction: a randomized clinical trial (EDIT-CMD)	Netherlands	2019	Diltiazem[b] Placebo	Normalization of at least one of the following: - IMR or - CFR or - Acetylcholine test	Yes. Severe renal impairment (eGFR < 30)
Randomized trial to examine a differential therapeutic response in symptomatic patients with nonobstructive coronary artery disease (EXAMINE-CAD)	Germany	2022	Bisoprolol Diltiazem Placebo	Change in angina symptom severity	Yes. Patients with renal failure (serum creatinine > 2 mg/dl)

ACEi, angiotensin-convert enzyme inhibitor; ARB, angiotension receptor blocker; CAD, coronary artery disease; CFR, coronary flow reserve; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IMR, index of microcirculatory resistance; MACE, major adverse cardiovascular event; MI, myocardial infarction.
[a]Statin doses atorvastatin 40-80 mg/d or rosuvastatin 20-40 mg.
[b]Diltiazem dose 120-360 mg.

consumption, decreasing workload, and improving CFR. Unfortunately, most ongoing clinical trials examining treatment efficacy in CMD exclude patients with chronic kidney disease (CKD) (Table 1).

It is well recognized that patients with CKD are at greater risk of cardiovascular events.[6] Conventional cardiovascular risk factors such as hypertension, hyperlipidemia, insulin resistance, and tobacco use are common not only in the development of CAD but also for CKD. These comorbid conditions not only lead to atherosclerosis but also to the progression of CKD as a result of their effect on both the large and small renal vasculature.[7] CKD leads to a chronic, systemic proinflammatory environment causing vascular and myocardial adaptations that contribute to the development of atherosclerosis, vascular calcification, vascular aging, and myocardial fibrosis.[7] These effects can be manifested as the structural abnormalities of the coronary microvasculature that can lead to CMD. Microvascular rarefaction distal to the level of smaller arterioles in patients with CKD and the development of endothelial dysfunction with diminished myocardial diffusion, in addition to the higher incidence of left ventricular hypertrophy and diastolic dysfunction, leads to compensatory vasodilation of arterioles, increased resting coronary flow, and depressed coronary circulatory reserve. Pharmacologic stress myocardial perfusion imaging studies are less accurate in patients with CKD, likely a result of high resting coronary flow.[6] Charytan *et al.*[8] previously reported that CFR as assessed by positron emission tomography was strongly associated with CKD stage and with cardiovascular mortality without evidence of effect modification by CKD. The study demonstrated that CFR was low in early-stage CKD without further decrease in end-stage renal disease, suggesting that the CKD physiology rather than the effects from hemodialysis was the primary driver of CMD.

In this issue of *KI Reports*, Park *et al.*[9] investigated the associations between invasive physiologic indices of CFR and IMR, CKD, and clinical outcomes of cardiac death and heart failure hospitalizations in 351 patients enrolled in the Prognostic Impact of Cardiac Diastolic Function and Coronary Microvascular Function registry. All patients underwent clinically-indicated invasive coronary angiography (analyzed at a core laboratory) and comprehensive physiologic assessments including fractional flow reserve, CFR and IMR measurements in at least 1 vessel. Only 42 patients (12%) in the study population had CKD, which was defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m^2 or with albuminuria for at least 3 months. As expected, patients with CKD had a higher prevalence of hypertension and diabetes and overall, most patients had earlier stage CKD with mean estimated glomerular filtration rate 62.2 $\pm$ 25.4 ml/min per 1.73 m^2. Patients included in the analysis were those with ejection fractions of at least 40% without concomitant severe valvular disease, those not requiring hemodialysis, and without physiologically significant obstructive coronary artery disease (fractional flow reserve >0.80).

Among the total cohort, 27.9% had reduced CFR. The reduced CFR group had lower resting distal arterial pressure or proximal aortic pressure and higher IMR value. Patients with CKD exhibited lower CFR than non-CKD patients, mainly because of increased resting coronary flow velocity. There was also no significant difference in angiographic disease

severity, hyperemic coronary flow, fractional flow reserve, and IMR between the 2 groups. There was no significant association between IMR and severity of CKD. Patients with CKD and those with reduced CFR, independently, more commonly showed signs of diastolic dysfunction as manifested by increased left ventricular wall thickness, left atrial volume index, increased E/e,' and increased RV systolic pressure.

The study demonstrated that CFR was associated with estimated glomerular filtration rate and the proportion of patients with reduced CFR was significantly increased with more advanced CKD stages. Eighteen patients with CKD (43%) and 59 non-CKD patients (22%) suffered a MACE respectively, primarily because of heart failure hospitalizations. The risk of cardiac death or heart failure hospitalization was lowest in patients without CKD and with preserved CFR (12.3%), and highest in those with CKD and reduced CFR (41.3%). In multivariable analysis, an abnormal CFR, CKD, and age were associated with MACE. An abnormal IMR was also associated with MACE but this was not statistically significant. The authors concluded that the severity of CKD is associated with CFR and that both CKD and depressed CFR were independently associated with a higher risk of cardiac death or hospitalization for heart failure at 3 years. In summary, the authors conclude that even patients with CKD with preserved left ventricular function and no obstructive coronary artery disease are at increased risk of MACE, and thus the assessment of microvascular dysfunction may help prognosticate these patients.

We commend the authors on their use of invasive assessment of coronary physiology including CFR and IMR in the study to shed light on the mechanism of reduced CFR in patients with CKD and excluding hemodynamically significant epicardial coronary artery disease. However, the inclusion of patients with advanced CKD is limited in this observational study. This may be a result of less patients with advanced CKD being referred for invasive coronary angiography because of the potential risks of contrast associated acute kidney injury. Nevertheless, it should be noted that the invasive physiologic assessments can be performed with little to no administration of contrast. It is well known via autopsy data of human and animal models that coronary microvascular remodeling, particularly rarefaction of capillaries, occurs in advanced stage CKD.[9] There is a paucity of data evaluating IMR in patients with CKD patients because prior studies exclusively used noninvasive parameters. As seen in Figure 3 in the original article by Park *et al.*,[9] published in *KI Reports*, there is a graded relationship between CKD stages and proportion of patients with IMR $\geq$25. The proportion of patients with CKD who had abnormal IMR were 15%, 20%, approximately 40%, and 50% in CKD stage 1, CKD stage 2, CKD stage 3, and in CKD stages 4 to 5, respectively, which correlated with a *P*-value for trend of 0.1, which is likely underpowered. In their multivariable analysis, an abnormal IMR $\geq$25 was also associated with MACE with a *P*-value of 0.093. Consequently, because of the limited number of patients with advanced CKD, the inference that CFR only but not IMR is impaired in CKD patients may not be accurate.

Although basic demographic data were available for the patients in this study, the proposed etiology for the development of CKD in these patients is not known. The heterogeneity in etiology could affect patient's individual prognosis. Certain inflammatory syndromes leading to renal disease may also affect the microvasculature at an accelerated rate. In addition, the prescribed medical therapy for these patients was not available. Prior studies in ischemia with nonobstructive coronary artery patients have demonstrated the beneficial role of beta blockers in modifying endothelial function, and statins and angiotensin-converting enzymes inhibitors in increasing CFR. Therefore, this information may be relevant for patient prognosis.[1] Although the study may be underpowered particularly for patients with advanced stages of CKD, it offers important insights into the mechanism and relationship between reduced CFR and CKD and the prognostic implications. Future larger studies including more patients with CKD are needed to verify these results to aid in-risk stratification for this high-risk cohort of patients.

DISCLOSURE

SB declares being on the addvisory board of Abbott Vascular, Boston Scientific, Biotronik, Amgen, Pfizer, Merck, REATA, Inari, and Truvic. All the other authors declared no competing interests.

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