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Research paper

Small vessel disease: Connections between the kidney and the heart

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ABSTRACT

Small vessel disease is characterized by global dysfunction of the microvascular system leading to reduced perfusion of various organ systems. The kidney is significantly vulnerable for microvascular dysfunction given its intricate capillary network and extensive endocrine influence. Studies have demonstrated a relationship between impaired renal function and small vessel disease in other organ systems, particularly the heart. Here we discuss the relationship between the kidney and the heart in the setting of microvascular dysfunction and identify areas of future study to better understand this relationship and potentially identify novel therapeutic strategies.

1. Introduction

Small vessel disease (SVD) is characterized by global dysfunction of the microvascular system leading to reduced perfusion of various organ systems. The organ systems affected by microvascular dysfunction involve those that receive substantial portions of cardiac output (brain, kidney, retina, *etc.*) and can present clinically as stroke, renal failure, blindness, ischemic heart disease, and dementia [1,2]. There are a variety of hypotheses regarding the global distribution of SVD, with some implicating individual organ systems and others indicating the presence of a systemic illness. In particular, the kidney is significantly involved in discussions surrounding microvascular dysfunction given its intricate capillary network and extensive endocrine influence. Several studies have demonstrated the relationship between impaired renal function and small vessel disease in other organ systems, with some of the clearest associations being between the kidney and the heart [3]. While the vast interplay of kidney and cardiovascular disease is a rapidly progressing area of study, examining this affiliation in regard to SVD could identify areas that merit further investigation. Here, we identify chronic kidney disease (CKD) as a microvascular disease, discuss the relationship between the kidney and the heart in the setting of microvascular dysfunction and identify areas of future study to better understand this relationship and potentially identify novel therapeutic strategies.

2. Chronic kidney disease: a microvascular disease

Kidney disease, including acute kidney injury (AKI), CKD, and end stage renal disease (ESRD) are among the top ten leading causes of death in the United States [4]. AKI has been found to occur in 20 % of all hospitalized patients and one-half of critically ill patients [5,6]. CKD affects 15 % of adults in the United States, costing Medicare $36 billion in 2017 [7,8]. The kidneys are a highly vascular organ that demonstrate serially connected capillary beds and receive 20 % of cardiac output. While this unique, autoregulatory microvasculature ensures physiologic renal function, it also creates susceptibility to ischemia. Therefore, diabetes, hypertension, and hyperlipidemia are vascular risk factors that have long been linked to kidney damage [8].

There are several factors involved in CKD that result in dysfunction of the microvascular system, but three critical areas have been identified: fibrotic remodeling, impaired vasoreactivity, and capillary rarefaction [8]. Fibrosis is characterized by an increase in extracellular matrix deposition that leads to an accumulation of nonfunctional tissue. Fibrotic remodeling in the kidney is a complex molecular process that involves several different cell types interacting at various levels of cellular structure. One of the cell types implicated is vascular pericytes, which possess the ability to differentiate into myofibroblasts; myofibroblasts deposit excessive extracellular matrix, which contributes to the development of fibrosis [9]. Indeed, in mice undergoing ureteral obstruction to induce renal fibrosis, vascular pericytes were identified as the primary source of myofibroblasts contributing to interstitial fibrosis [10]. While the specific mechanisms involved in renal fibrosis remain unclear, this differentiation of pericytes into myofibroblasts demonstrates how chronic kidney disease can result in an environment that leads to dysfunction of the local microvascular system.

Additionally, kidney disease has been associated with a loss of

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vasoreactivity. Compromised renal vasoreactivity has been identified in a variety of acute kidney injuries including calcineurin toxicity, contrast-induced acute kidney injury, and hepatorenal syndrome [11–13]. Similar to other capillary networks, endothelial nitric oxide synthase (eNOS) plays a primary role in reducing shear stress in the renal microvasculature by facilitating flow-mediated dilation [14,15]. Interestingly, hypertensive patients with reduced eGFR and decreased coronary flow velocity reserve were associated with increased levels of asymmetric dimethylarginine (ADMA) when compared to hypertensive patients with normal renal function [16]. ADMA is an endogenous inhibitor of nitric oxide synthase that has been associated with endothelial dysfunction and has been shown to increase with worsening renal function [17,18]. Loss of vasoreactivity in the kidney can further progression of renal disease by predisposing to hemodynamic instability and metabolic imbalance. These studies demonstrate the presence of impaired vasoreactivity in CKD and highlight the importance of endothelial dysfunction in its pathogenesis.

Another critical aspect that demonstrates the connection between CKD and microvascular dysfunction is capillary rarefaction. Capillary rarefaction is characterized by structural and/or functional loss of the small vessels and is present in CKD [19]. Vascular endothelial growth factor (VEGF) is an angiogenic molecule that has a critical role in maintaining the integrity of microvascular networks throughout the body, including the kidney. In patients with a variety of glomerular diseases, VEGF-expressing cells were decreased or absent in areas of glomerular sclerosis [20]. This loss of renal VEGF further exemplifies how kidney disease can interfere with signaling pathways involved in the maintenance of the microvasculature.

Historically, decreased renal function as a result of compromised perfusion was thought to be caused by hypotension or obstruction of the large renal vessels. However, a meta-analysis encompassing seven randomized controlled trials demonstrated that in patients with atherosclerotic renal artery stenosis revascularization was not superior to medical therapy regarding any outcome, including renal events and myocardial infarction [21]. These findings establish an important distinction: macrovascular disease does not fully explain the renal impairments seen in kidney disease. Dysfunction of the dense capillary network present in the kidney is a complicated pathophysiologic process that contributes to worsening renal function and potentially has effects on other organ systems.

3. CKD and coronary microvascular dysfunction

The relationship between CKD and cardiovascular disease is extensively documented, with cardiovascular death accounting for nearly 50 % of mortality in patients with CKD compared to 25 % in patients with normal renal function [22]. Additionally, patients with CKD are six times more likely to die of cardiovascular event than progress to end stage renal disease, and this increased risk is not completely explained by the presence of traditional risk factors [23]. Further, the association between cardiac events and CKD is evident even in patients without existing coronary vessel disease [23,24]. Therefore, it has been suggested that microvascular dysfunction could be the etiology linking these two disease processes. The studies linking CKD and coronary microvascular dysfunction are listed in Table 1.

Currently, there is no widely accepted *in vivo* measure of renal microvasculature capacity; however, estimated glomerular filtration rate (eGFR) can serve as an estimation of renal function and thus microvasculature damage. Coronary flow reserve is a measure of coronary artery vasodilation that is widely used to evaluate coronary microvascular function. Several studies have demonstrated the association between CKD and low coronary flow reserve (CFR), which is a strong predictor of cardiovascular mortality [25–27]. Interestingly, in patients without obstructive coronary artery disease, those with CKD had decreased CFR compared to those with a normal GFR [26]. Similarly, Charytan et al. found a progressive decrease in CFR with an increase in severity of CKD, with a 23 % lower CFR in patients with dialysis-dependent CKD [27]. Further, coronary flow reserve is a risk factor for coronary events in patients with CKD, independent of traditional risk factors [28]. Taken together, these studies establish the presence of coronary microvascular dysfunction in patients with CKD, and microvascular dysfunction might explain the increased risk of cardiovascular events in CKD (Fig. 1).

4. Microvascular dysfunction in CKD: cause or consequence?

While microvascular dysfunction is clearly present in CKD, the question remains whether CKD causes dysfunction of the coronary microvasculature or both kidney disease and coronary microvascular dysfunction reflect global dysfunction of the microvasculature. A recent literature review presents substantial evidence that microvascular dysfunction is a systemic process that concomitantly affects multiple

Table 1
References demonstrating association of CKD and CMD in the absence of obstructive CAD.

Reference	Design	Population	Measurement of CFR	Key findings
Sakamoto et al. [25]	Prospective Cohort	Patients without obstructive CAD or vasospasm (N = 73, CKD = 13)	Intracoronary papaverine	CFR was significantly lower in patients with CKD compared to controls; low CFR and CKD were associated with increased cardiocerebrovascular events
Chade et al. [26]	Cross-sectional	Patients without CAD referred for angiography (N = 605, CKD = 124)	Intracoronary adenosine	Decreased GFR was associated with low CFR
Nelson et al. [54]	Cross-sectional	ESRD patients without obstructive CAD (N = 30, ESRD = 15)	Intracoronary adenosine	Patients with ESRD had a reduced CFR
Kashioulas et al. [55]	Cross-sectional	CKD 3 and 4 patients without a diagnosis of heart disease (N = 132, CKD = 91)	Intracoronary adenosine	CKD patients had significantly reduced CFVR compared to controls
Fukushima et al. [56]	Cross-sectional	CKD patients with normal LV function and coronary artery flow (N = 82, CKD = 40)	Stress ^{82}Rb PET/CT (dipyridamole)	Global MFR was reduced in patients with CKD compared to controls
Tsuda et al. [57]	Cross-sectional	CKD patients without heart disease or CAD (N = 92, CKD = 46)	Stress SPECT-MPI (adenosine)	CKD patients had a lower MPR index compared to controls
Yilmaz and Yalta [58]	Cross-sectional	Patients with decreased GFR and normal coronary arteries (N = 207, CKD = 105)	Thrombolysis in myocardial infarction (TIMI) frame count	Decreased GFR was associated with decreased coronary flow
Ragosta et al. [59]	Cross-sectional	Patients with diabetic nephropathy without CAD (N = 64, CKD = 21)	Doppler ultrasound scanning wire	Patients with diabetes and renal failure were more likely to have abnormal CVR

CKD: chronic kidney disease; CMD: coronary microvascular dysfunction; CAD: coronary artery disease; CFR: coronary flow reserve; GFR: glomerular filtration rate; ESRD: end stage renal disease; CFVR: coronary flow velocity reserve; LV: left ventricular; MFR: myocardial flow reserve; MPR: myocardial perfusion reserve; CVR: coronary velocity reserve.

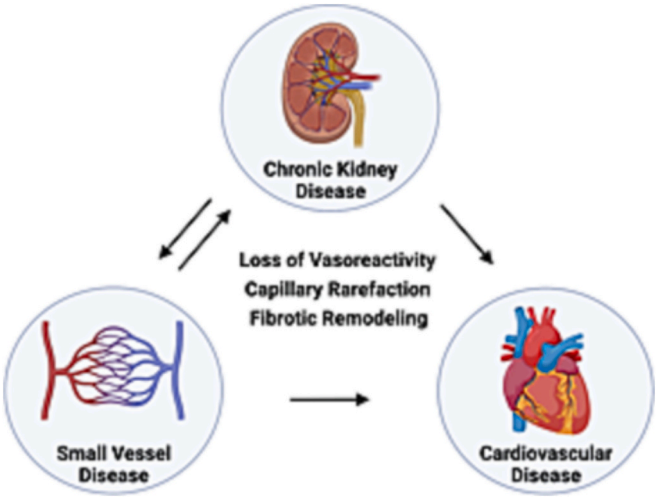

Fig. 1. Bidirectional relationship between CKD and small vessel disease.

organ systems [3]. The evidence includes a number of clinical studies demonstrating that clinical presentation of microvascular dysfunction in one organ system is often accompanied by subclinical or overt microvascular dysfunction of other organ systems. In support of this hypothesis, abnormalities of 16 biomarkers reflecting systemic disease were found in the setting of isolated microvasculature dysfunction of the heart, kidney, and brain [29]. Even genetic disorders which predominantly affect one organ system demonstrate evidence of subclinical microvascular dysfunction in other organs [30,31]. Several large prospective cohort studies have shown that changes in the retinal vasculature independently predict the development of incident CKD and worsening renal function [32–34]. Taken together, these papers provide an overabundance of evidence that demonstrate the systemic nature of microvascular disease, suggesting that CKD is a consequence of global small vessel impairment. Contrarily, several studies exist that implicate CKD as the causative force for microvascular dysfunction in other organs. Utilizing two experimental mouse models of uremic CKD, Prommer et al. demonstrated microvascular rarefaction in the heart and cremaster muscle that was dependent on serum urea levels [35]. The microvascular damage in the myocardium and cremaster preceded any macrovascular pathology and increased with severity of renal disease. These observations suggest that CKD can lead to microvascular dysfunction in distant organs. Several other studies have shown that experimental CKD is associated with microvascular rarefaction of the myocardium and is unaffected by hypertension or antihypertensive therapy [36,37]. Sympathetic hyperactivity, up-regulation of calcineurin signaling pathways, dysfunction of bone marrow derived progenitor cells and endothelin have been proposed to mediate some of these effects [36,38–40]. Interestingly, we have shown in women with ischemia and non-obstructive coronary angiograms, decreased coronary flow reserve is associated with dysfunction of bone marrow derived angiogenic cells [41]. Thus, CKD and microvascular dysfunction might have a bidirectional relationship, where CKD can cause microvascular dysfunction and systemic microvascular dysfunction can lead to CKD (Fig. 1).

5. Diagnosis of renal microvascular dysfunction

Experimental studies have relied on enumerating microvascular density to quantify microvascular rarefaction or arterial myography to examine vasoreactivity *ex vivo*. Computed tomography (CT) and magnetic resonance imaging (MRI) are both widely used imaging techniques that have proven to be extremely effective in clinical practice to evaluate structural defects in the kidneys. However, they lack the resolution for imaging microvasculature *in vivo*. Blood oxygen level dependent (BOLD) MRI determines vessel functionality by measuring the oxygenation state of the tissues. While BOLD MRI is a useful technique, it is indirect and can only detect vascular dysfunction in areas where established pathology is already present, limiting its potential to monitor alterations in the microvasculature prior to pathology [42]. Thus, these imaging methods have obvious limitations and are not readily applicable to the clinical setting to measure renal microvascular function. The renal flow reserve, the difference between stress and basal flow, has been proposed as a marker of renal microvascular function [43]. However, unlike coronary flow reserve, the methodology has not been standardized or shown to be predictive of either cardiac or renal outcomes in prospective studies. The renal resistive index at the level of the arcuate arteries can be measured by ultrasound and is defined as the (peak systolic velocity − end diastolic velocity) / peak systolic velocity. Although it is often impaired in microvascular dysfunction, an abnormal resistive index is not specific and might reflect central hemodynamic characteristics rather than that of the renal microcirculation.

6. Treatment of microvascular dysfunction

While treatment of atherosclerosis is driven by data from randomized controlled trials and guidelines from professional societies, whether these interventions are effective for microvascular dysfunction is uncertain. The ENDOFIND study is currently evaluating the role of endothelial dysfunction in the pathogenesis of microvascular dysfunction and the effect of intensive medical management on decreasing adverse outcomes in such patients [44]. Biological sex and age are powerful modulators of coronary microvascular function and women have traditionally been underrepresented in most clinical trials. The WARRIOR trial is specifically recruiting women with microvascular dysfunction to determine how intense medical management will modulate outcomes in women with coronary microvascular dysfunction [45]. Anti-inflammatory agents such as IL-1β and IL-6 antagonists have shown to be efficacious in the treatment of coronary atherosclerosis, while others such as methotrexate have been disappointing [46–48]. Inflammation has been implicated in the pathogenesis of microvascular dysfunction. Given the complexities in inflammatory pathways and heterogeneity in treatment responses, these agents need to be evaluated in patients with microvascular dysfunction. A few agents that specifically target the microvasculature have shown promise in experimental studies. In AKI, decreased levels of VEGF are associated with increased capillary rarefaction and associate negatively with chances of renal recovery [49]. While randomized controlled trials in humans are lacking, studies in a porcine model of renal artery stenosis demonstrated that intrarenal infusion of VEGF preserved renal microvasculature and function [50]. The lack of therapies targeting microvascular dysfunction in the kidney highlights the need for more preclinical studies investigating the mechanistic causes associated with the dysfunction of renal microvascular network in CKD.

7. Knowledge gaps

Ample evidence exists for microvascular dysfunction in kidney disease and its association with adverse outcomes. However, these studies rely on detection of microvascular dysfunction in distant, more accessible, vascular beds such as the eye, oral mucosa or skin. There are structural and functional differences between microvasculature in different organs and dysfunction in one organ does not imply dysfunction in another. One major knowledge gap is the lack of non-invasive *in vivo* imaging modalities to longitudinally monitor microvascular changes in the kidney. Advances in ultrasound (US) imaging technology provide the most promising developments in monitoring renal microvasculature. Contrast-enhanced ultrafast Doppler US is a relatively novel imaging technique that uses microbubbles to enhance images and has been shown to accurately predict the progression from AKI to CKD following ischemic AKI in an ischemia/reperfusion injury mouse model

[51]. This novel US technique has potential to serve as a method of monitoring renal microvasculature in patients at risk of developing CKD, although it needs to be validated in future clinical studies of human subjects before it can be adopted to clinical practice.

Serum creatinine, and presence of microalbuminuria are used to establish a diagnosis of CKD. However, these assays lack sensitivity and novel biomarkers that can detect mild renal dysfunction is necessary to facilitate early intervention and to prevent progressive kidney disease. Several studies have demonstrated cystatin C to be a better predictor of outcomes and have stronger associations with CKD than serum creatinine [52]. In a study of elderly patients without CKD, serum cystatin C levels had stronger associations with all-cause mortality and cardiovascular events than serum creatinine; also patients with elevated cystatin C levels had a 4-fold increased risk for developing CKD when compared to those with normal cystatin C levels [53]. This study demonstrates the potential of cystatin C to serve as a biomarker for patients who have preclinical kidney disease. Whether cystatin C is a marker for microvascular dysfunction is an intriguing possibility that remains to be tested.

While it is evident that CKD can cause microvascular dysfunction, the molecular pathways leading to microvascular dysfunction in distant organs is unclear and has hampered development of specific therapeutic agents. Accumulation of uremic toxins, endocrine or metabolic changes, sympathetic activation, impaired function of bone marrow derived angiogenic cells and circadian dysfunction all have been postulated as possible contributors to microvascular dysfunction. However, rodent models of CKD have shown limited potential for translation to human disease. The use of large animal models and validation of putative targets in human tissues might help us uncover pathways that are more relevant to human disease.

8. Perspectives

CKD is a microvascular disease that is characterized by fibrotic remodeling, impaired vasoreactivity, and microvascular rarefaction. While the epidemiological link between CKD and CVD is well studied, microvascular dysfunction could prove to be one of the pathophysiologic links between these two common diseases. Further study into the question of whether CKD is a cause or consequence of global impaired microvasculature is warranted and could provide mechanistic insights to guide treatment decisions and devise new trials to discover novel therapeutics. Additionally, several knowledge gaps exist in regard to imaging of the renal microvasculature, biomarkers to determine early-stage CKD, and signaling pathways mediating microvascular dysfunction and addressing these knowledge gaps could provide improved outcomes in this patient population.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] C.S. Thompson, A.M. Hakim, Living beyond our physiological means, Stroke 40 (2009) 5, https://doi.org/10.1161/STROKEAHA.108.542266.

[2] A.M. Hakim, Small vessel disease, Front. Neurol. 10 (SEP) (2019), https://doi.org/10.3389/FNEUR.2019.01020.

[3] D.S. Feuer, E.M. Handberg, B. Mehrad, et al., Microvascular dysfunction as a systemic disease: a review of the evidence, Am. J. Med. (2022), https://doi.org/10.1016/J.AMJMED.2022.04.006.

[4] S.L. Murphy, J. Xu, K.D. Kochanek, E. Arias, Mortality in the United States, 2020, NCHS Data Brief 328 (2020) 1–8.

[5] P. Susantitaphong, D.N. Cruz, J. Cerda, et al., World incidence of AKI: a meta-analysis, Clin. J. Am. Soc. Nephrol. 8 (9) (2013) 1482–1493, https://doi.org/10.2215/CJN.00710113.

[6] S.A. Silver, W. Beaubien-Souligny, P.S. Shah, et al., The prevalence of acute kidney injury in patients hospitalized with COVID-19 infection: a systematic review and meta-analysis, Kidney Med. 3 (1) (2021) 83–98.e1, https://doi.org/10.1016/J.XKME.2020.11.008.

[7] Chronic Kidney Disease in the United States. https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html, 2021. Accessed July 17, 2022.

[8] S. Krishnan, A.D. Suarez-Martinez, P. Bagher, et al., Microvascular dysfunction and kidney disease: challenges and opportunities? Microcirculation 28 (3) (2021) https://doi.org/10.1111/MICC.12661.

[9] I. Shaw, S. Rider, J. Mullins, J. Hughes, B. Péault, Pericytes in the renal vasculature: roles in health and disease, Nat. Rev. Nephrol. 14 (8) (2018) 521–534, https://doi.org/10.1038/S41581-018-0032-4.

[10] S.L. Lin, T. Kisseleva, D.A. Brenner, J.S. Duffield, Pericytes and perivascular fibroblasts are the primary source of collagen-producing cells in obstructive fibrosis of the kidney, Am. J. Pathol. 173 (6) (2008) 1617–1627, https://doi.org/10.2353/AJPATH.2008.080433.

[11] B.M. Murray, M.S. Paller, T.F. Ferris, Effect of cyclosporine administration on renal hemodynamics in conscious rats, Kidney Int. 28 (5) (1985) 767–774, https://doi.org/10.1038/KI.1985.196.

[12] S.N. Heyman, M. Brezis, C.A. Reubinoff, et al., Acute renal failure with selective medullary injury in the rat, J. Clin. Invest. 82 (2) (1988) 401–412, https://doi.org/10.1172/JCI113612.

[13] M.C. Kew, R.R. Varma, H.S. Williams, P.W. Brunt, K.J. Hourigan, S. Sherlock, Renal and intrarenal blood-flow in cirrhosis of the liver, Lancet 2 (7723) (1971) 504–510, https://doi.org/10.1016/S0140-6736(71)90435-1.

[14] J. Pittner, M. Wolgast, D. Casellas, A.E.G. Persson, Increased shear stress-released NO and decreased endothelial calcium in rat isolated perfused juxtamedullary nephrons, Kidney Int. 67 (1) (2005) 227–236, https://doi.org/10.1111/J.1523-1755.2005.00073.X.

[15] L.A. Juncos, J. Garvin, O.A. Carretero, S. Ito, Flow modulates myogenic responses in isolated microperfused rabbit afferent arterioles via endothelium-derived nitric oxide, J. Clin. Invest. 95 (6) (1995) 2741, https://doi.org/10.1172/JCI117977.

[16] H. Fujii, S. Takiuchi, Y. Kawano, M. Fukagawa, Putative role of asymmetric dimethylarginine in microvascular disease of kidney and heart in hypertensive patients, Am. J. Hypertens. 21 (6) (2008) 650–656, https://doi.org/10.1038/AJH.2008.29/2/M_AJH.650.T2.JPEG.

[17] S. Takiuchi, H. Fujii, K. Kamide, et al., Plasma asymmetric dimethylarginine and coronary and peripheral endothelial dysfunction in hypertensive patients, Am. J. Hypertens. 17 (9) (2004) 802–808, https://doi.org/10.1016/J.AMJHYPER.2004.05.005.

[18] J.T. Kielstein, R.H. Boger, S.M. Bode-Boger, et al., Asymmetric dimethylarginine plasma concentrations differ in patients with end-stage renal disease: relationship to treatment method and atherosclerotic disease, J. Am. Soc. Nephrol. 10 (3) (1999) 594–600, https://doi.org/10.1681/ASN.V103594.

[19] B. Afsar, R.E. Afsar, T. Dagel, et al., Capillary rarefaction from the kidney point of view, Clin. Kidney J. 11 (3) (2018) 295–301, https://doi.org/10.1093/CKJ/SFX133.

[20] K. Shulman, S. Rosen, K. Tognazzi, E.J. Manseau, L.F. Brown, Expression of vascular permeability factor (VPF/VEGF) is altered in many glomerular diseases, J. Am. Soc. Nephrol. 7 (5) (1996) 661–666, https://doi.org/10.1681/ASN.V75661.

[21] I.B. Riaz, M. Husnain, H. Riaz, et al., Meta-analysis of revascularization versus medical therapy for atherosclerotic renal artery stenosis, Am. J. Cardiol. 114 (7) (2014) 1116–1123, https://doi.org/10.1016/J.AMJCARD.2014.06.033.

[22] J. Jankowski, J. Floege, D. Fliser, M. Böhm, N. Marx, Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options, Circulation 143 (11) (2021) 1157–1172, https://doi.org/10.1161/CIRCULATIONAHA.120.050686.

[23] L.S. Dalrymple, R. Katz, B. Kestenbaum, et al., Chronic kidney disease and the risk of end-stage renal disease versus death, J. Gen. Intern. Med. 26 (4) (2011) 379–385, https://doi.org/10.1007/S11606-010-1511-X.

[24] D.E. Weiner, S. Tabatabai, H. Tighiouart, et al., Cardiovascular outcomes and all-cause mortality: exploring the interaction between CKD and cardiovascular disease, Am. J. Kidney Dis. 48 (3) (2006) 392–401, https://doi.org/10.1053/J.AJKD.2006.05.021.

[25] N. Sakamoto, S. Iwaya, T. Owada, et al., A reduction of coronary flow reserve is associated with chronic kidney disease and long-term cardio-cerebrovascular events in patients with non-obstructive coronary artery disease and vasospasm, Fukushima J. Med. Sci. 58 (2) (2012) 136–143, https://doi.org/10.5387/FMS.58.136.

[26] A.R. Chade, D. Brosh, S.T. Higano, R.J. Lennon, L.O. Lerman, A. Lerman, Mild renal insufficiency is associated with reduced coronary flow in patients with non-obstructive coronary artery disease, Kidney Int. 69 (2) (2006) 266–271, https://doi.org/10.1038/SJ.KI.5000031.

[27] D.M. Charytan, H. Skali, N.R. Shah, et al., Coronary flow reserve is predictive of the risk of cardiovascular death regardless of chronic kidney disease stage, Kidney Int. 93 (2) (2018) 501–509, https://doi.org/10.1016/J.KINT.2017.07.025.

[28] K. Nakanishi, S. Fukuda, K. Shimada, et al., Prognostic value of coronary flow reserve on long-term cardiovascular outcomes in patients with chronic kidney disease, Am. J. Cardiol. 112 (7) (2013) 928–932, https://doi.org/10.1016/J.AMJCARD.2013.05.025.

[29] A. Nowroozpoor, D. Gutterman, B. Safdar, Is microvascular dysfunction a systemic disorder with common biomarkers found in the heart, brain, and kidneys? — a scoping review, Microvasc. Res. 134 (2021), 104123, https://doi.org/10.1016/J.MVR.2020.104123.

[30] A. Argirò, R. Sciagrà, A. Marchi, et al., Coronary microvascular function is impaired in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, Eur. J. Neurol. 28 (11) (2021) 3809–3813, https://doi.org/10.1111/ENE.14678.

[31] S.A.J. Lesnik Oberstein, J.W. Jukema, S.G. van Duinen, et al., Myocardial infarction in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Medicine 82 (4) (2003) 251–256, https://doi.org/10.1097/01.MD.0000085054.63483.40.
[32] M.S. Edwards, D.B. Wilson, T.E. Craven, et al., Associations between retinal microvascular abnormalities and declining renal function in the elderly population: the cardiovascular health study, Am. J. Kidney Dis. 46 (2) (2005) 214–224, https://doi.org/10.1053/J.AJKD.2005.05.005.
[33] J.W.Y. Yau, J. Xie, R. Kawasaki, et al., Retinal arteriolar narrowing and subsequent development of CKD stage 3: the multi-ethnic study of atherosclerosis (MESA), Am. J. Kidney Dis. 58 (1) (2011) 39–46, https://doi.org/10.1053/J.AJKD.2011.02.382.
[34] T.Y. Wong, J. Coresh, R. Klein, et al., Retinal microvascular abnormalities and renal dysfunction: the atherosclerosis risk in communities study, J. Am. Soc. Nephrol. 15 (9) (2004) 2469–2476, https://doi.org/10.1097/01.ASN.0000136133.28194.E4.
[35] H.U. Prommer, J. Maurer, K. Von Websky, et al., Chronic kidney disease induces a systemic microangiopathy, tissue hypoxia and dysfunctional angiogenesis, Sci. Rep. 8 (1) (2018), https://doi.org/10.1038/S41598-018-23663-1.
[36] K. Amann, G. Odoni, K. Benz, et al., Sympathetic blockade prevents the decrease in cardiac VEGF expression and capillary supply in experimental renal failure, Am. J. Physiol. Renal. Physiol. 300 (1) (2011), https://doi.org/10.1152/AJPRENAL.00363.2010.
[37] J. Törnig, K. Amann, E. Ritz, C. Nichols, M. Zeier, G. Mall, Arteriolar wall thickening, capillary rarefaction and interstitial fibrosis in the heart of rats with renal failure:the effects of ramipril, nifedipine and moxonidine, J. Am. Soc. Nephrol. 7 (5) (1996) 667–675, https://doi.org/10.1681/ASN.V75667.
[38] G.S. Di Marco, S. Reuter, D. Kentrup, et al., Cardioprotective effect of calcineurin inhibition in an animal model of renal disease, Eur. Heart J. 32 (15) (2011) 1935–1945, https://doi.org/10.1093/EURHEARTJ/EHQ436.
[39] L. Golle, H.U. Gerth, K. Beul, et al., Bone marrow-derived cells and their conditioned medium induce microvascular repair in uremic rats by stimulation of endogenous repair mechanisms, Sci. Rep. 7 (1) (2017), https://doi.org/10.1038/S41598-017-09883-X.
[40] K. Amann, K. Münter, S. Wessels, et al., Endothelin a receptor blockade prevents capillary/myocyte mismatch in the heart of uremic animals, J Am Soc Nephrol. 11 (9) (2000) 1702–1711, https://doi.org/10.1681/ASN.V1191702.
[41] R. Mohandas, L. Sautina, S. Li, et al., Number and function of bone-marrow derived angiogenic cells and coronary flow reserve in women without obstructive coronary artery disease: a substudy of the NHLBI-sponsored women's ischemia syndrome evaluation (WISE), PLoS One 8 (12) (2013), https://doi.org/10.1371/JOURNAL.PONE.0081595.
[42] M. Dujardin, S. Sourbron, R. Luypaert, D. Verbeelen, T. Stadnik, Quantification of renal perfusion and function on a voxel-by-voxel basis: a feasibility study, Magn. Reson. Med. 54 (4) (2005) 841–849, https://doi.org/10.1002/MRM.20608.
[43] G. Manoharan, N.H.J. Pijls, N. Lameire, et al., Assessment of renal flow and flow reserve in humans, J. Am. Coll. Cardiol. 47 (3) (2006) 620–625, https://doi.org/10.1016/J.JACC.2005.08.071.
[44] H. Liu, G. Xie, W. Huang, et al., Rationale and design of a multicenter, randomized, patients-blinded two-stage clinical trial on effects of endothelial function test in patients with non-obstructive coronary artery disease (ENDOFIND), Int. J. Cardiol. 325 (2021) 16–22, https://doi.org/10.1016/J.IJCARD.2020.10.033.
[45] E.M. Handberg, C.N.B. Merz, R.M. Cooper-Dehoff, et al., Rationale and design of the women's ischemia trial to reduce events in nonobstructive CAD (WARRIOR) trial, Am. Heart J. 237 (2021) 90–103, https://doi.org/10.1016/J.AHJ.2021.03.011.
[46] P.M. Ridker, B.M. Everett, T. Thuren, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease, N. Engl. J. Med. 377 (12) (2017) 1119–1131, https://doi.org/10.1056/NEJMOA1707914.
[47] K. Broch, A.K. Anstensrud, S. Woxholt, et al., Randomized trial of Interleukin-6 receptor inhibition in patients with acute ST-segment elevation myocardial infarction, J. Am. Coll. Cardiol. 77 (15) (2021) 1845–1855, https://doi.org/10.1016/J.JACC.2021.02.049.
[48] P.M. Ridker, B.M. Everett, A. Pradhan, et al., Low-dose methotrexate for the prevention of atherosclerotic events, N. Engl. J. Med. 380 (8) (2019) 752–762, https://doi.org/10.1056/NEJMOA1809798.
[49] S.G. Mansour, W.R. Zhang, D.G. Moledina, et al., The association of angiogenesis markers with acute kidney injury and mortality after cardiac surgery, Am. J. Kidney Dis. 74 (1) (2019) 36–46, https://doi.org/10.1053/J.AJKD.2019.01.028.
[50] R. Iliescu, S.R. Fernandez, S. Kelsen, C. Maric, A.R. Chade, Role of renal microcirculation in experimental renovascular disease, Nephrol. Dial. Transplant. 25 (4) (2010) 1079–1087, https://doi.org/10.1093/NDT/GFP605.
[51] W. Cao, S. Cui, L. Yang, et al., Contrast-enhanced ultrasound for assessing renal perfusion impairment and predicting acute kidney injury to chronic kidney disease progression, Antioxid. Redox Signal. 27 (17) (2017) 1397–1411, https://doi.org/10.1089/ARS.2017.7006.
[52] S. Lopez-Giacoman, M. Madero, Biomarkers in chronic kidney disease, from kidney function to kidney damage, World J. Nephrol. 4 (1) (2015) 57, https://doi.org/10.5527/WJN.V4.I1.57.
[53] M.G. Shlipak, R. Katz, M.J. Sarnak, et al., Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease, Ann. Intern. Med. 145 (4) (2006) 237–246, https://doi.org/10.7326/0003-4819-145-4-200608150-00003.
[54] A.J. Nelson, B.K. Dundon, S.G. Worthley, et al., End-stage renal failure is associated with impaired coronary microvascular function, Coron. Artery Dis. 30 (7) (2019) 520–527, https://doi.org/10.1097/MCA.0000000000000727.
[55] P. Kashioulis, C.W. Guron, M.K. Svensson, O. Hammarsten, A. Saeed, G. Guron, Patients with moderate chronic kidney disease without heart disease have reduced coronary flow velocity reserve, ESC Hear. Fail. 7 (5) (2020) 2797–2806, https://doi.org/10.1002/EHF2.12878.
[56] K. Fukushima, M.S. Javadi, T. Higuchi, et al., Impaired global myocardial flow dynamics despite Normal left ventricular function and regional perfusion in chronic kidney disease: a quantitative analysis of clinical 82Rb PET/CT studies, J. Nucl. Med. 53 (6) (2012) 887–893, https://doi.org/10.2967/JNUMED.111.099325.
[57] N. Tsuda, S. Shiraishi, F. Sakamoto, et al., Quantification of myocardial perfusion reserve using dynamic SPECT images of patients with chronic kidney disease, J. Cardiol. 71 (2) (2018) 174–180, https://doi.org/10.1016/J.JJCC.2017.07.009.
[58] M. Birhan Yilmaz, K. Yalta, Coronary flow slows as renal function worsens, Clin. Cardiol. 32 (5) (2009) 278–282, https://doi.org/10.1002/CLC.20387.
[59] M. Ragosta, H. Samady, R.B. Isaacs, L.W. Gimple, I.J. Sarembock, E.R. Powers, Coronary flow reserve abnormalities in patients with diabetes mellitus who have end-stage renal disease and normal epicardial coronary arteries, Am. Heart J. 147 (6) (2004) 1017–1023, https://doi.org/10.1016/J.AHJ.2003.07.029.