REVIEW

THE AMERICAN JOURNAL of MEDICINE®

# Microvascular Dysfunction as a Systemic Disease: A Review of the Evidence

**Daniel S. Feuer, BS,[a] Eileen M. Handberg, PhD,[a,b] Borna Mehrad, MD,[a,c] Janet Wei, MD,[d] C. Noel Bairey Merz, MD,[d] Carl J. Pepine, MD,[a,b] Ellen C. Keeley, MD, MS[a,b]**

*[a]Department of Medicine; [b]Division of Cardiovascular Medicine; [c]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Florida, Gainesville; [d]Barbra Streisand Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, Calif.*

## ABSTRACT

Microvascular dysfunction describes a varied set of conditions that includes vessel destruction, abnormal vasoreactivity, in situ thrombosis, and fibrosis, which ultimately results in tissue damage and progressive organ failure. Microvascular dysfunction has a wide array of clinical presentations, ranging from ischemic heart disease to renal failure, stroke, blindness, pulmonary arterial hypertension, and dementia. An intriguing unifying hypothesis suggests that microvascular dysfunction of specific organs is an expression of a systemic illness that worsens with age and is accelerated by vascular risk factors. Studying relationships across a spectrum of microvascular diseases affecting the brain, retina, kidney, lung, and heart may uncover shared pathologic mechanisms that could inform novel treatment strategies. We review the evidence that supports the notion that microvascular dysfunction represents a global pathologic process. Our focus is on studies reporting concomitant microvascular dysfunction of the heart with that of the brain, kidney, retina, and lung.

 *• The American Journal of Medicine (2022) 135:1059–1068*

**KEYWORDS:** Coronary microvascular dysfunction; Microvascular dysfunction; Small vessel disease

## INTRODUCTION

The human microcirculation is tasked with the delivery of oxygen and nutrients and removal of cellular waste products in the left-sided circulation, and with gas exchange in the pulmonary circulation.[1] Microvascular dysfunction describes a varied set of conditions that cause small vessel obstruction, resulting in tissue damage and organ dysfunction. Microvascular dysfunction has a wide array of clinical presentations, ranging from ischemic heart disease to renal failure, stroke, blindness, pulmonary hypertension, and dementia.[2] This concept was introduced more than 30 years ago in a study demonstrating that patients with angina and normal epicardial coronary arteries had a systemic abnormality in their vasodilator reserve.[3] An intriguing unifying hypothesis suggests that microvascular dysfunction of specific organs is an expression of a systemic illness that worsens with age and is accelerated by vascular risk factors.[2] In support of this hypothesis, microvascular dysfunction of the heart and brain may share a common pathophysiology.[4-6] Studying relationships across a spectrum of microvascular diseases affecting the brain, retina, kidney, lung, and heart may uncover shared pathologic mechanisms that could

**Funding:** This work was supported by Department of Defense-funded WARRIOR trial [W81XWH-17-2-0030] (CJP), the McJunkin Family Foundation for the WARRIOR Biorepository (CJP), the American Heart Association [18TPA34170486] (BM), and by contracts from the National Heart, Lung and Blood Institutes nos. R01 HL153500 (Wei), R01 AI135128 (BM), and N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, grants U0164829, U01 HL649141, U01 HL649241, K23 HL125941, T32 HL69751, R01 HL090957, 1R03 AG032631, R01 HL146158, R01 HL124649, PR150224P1 (CDMRP-DoD), U54 AG065141, GCRC grant M01-RR00425 from the National Center for Research Resources, the National Center for Advancing Translational Sciences Grant UL1TR000124, the Barbra Streisand Women's Cardiovascular Research and Education Program, and the Erika J. Glazer Women's Heart Research Initiative, Cedars-Sinai Medical Center, Los Angeles (CNBM).

**Conflicts of Interest:** CNBM has disclosures from iRhythm. JW has disclosures from Abbott Vascular. The other authors do not have conflict of interest.

**Authorship:** All authors had access to the data and a role in writing the manuscript.

Requests for reprints should be addressed to Ellen C. Keeley, MD, MS, Division of Cardiovascular Medicine, University of Florida, 1600 SW Archer Road, P.O. Box 100277, Gainesville, FL 32610-0277.

E-mail address: Ellen.Keeley@medicine.ufl.edu

0002-9343/
https://doi.org/10.1016/j.amjmed.2022.04.006

inform novel treatment strategies. We review the evidence supporting microvascular dysfunction as a global pathologic process, specifically focused on concomitant presentation of microvascular dysfunction of the heart and other organs (Figure).

## METHODS

We performed a literature search using PubMed and EMBASE for articles pertaining to simultaneous microvascular dysfunction of the heart with microvascular dysfunction of another organ, specifically, the brain, kidney, retina, and lung. Search terms for microvascular dysfunction of the heart ("microvascular angina" or "syndrome X" or "coronary microvascular dysfunction" or "coronary flow reserve" or "myocardial perfusion" or "normal coronary" or "coronary vasoreactivity" or "nonobstructive coronary") were combined with search terms for microvascular dysfunction of the brain (brain or cerebral or cerebrovascular or "small-vessel disease" or lipohyalinosis or "cerebral amyloid angiopathy" or lacunar; yielded 835 results), kidney (chronic kidney disease or renal or nephropathy or nephr* or "end-stage kidney disease" or "end-stage renal disease"; yielded 886 results), lung ("pulmonary hypertension" or "PAH" or "pulmonary vascular resistance" or "pulmonary artery pressure" or "Woods units"; yielded 158 results), and retina (retina or retin* or retinopathy or retinitis or vision or eye or ocular; yielded 239 results). Our literature search, including search terms, was guided by the Associate University Librarian of the Health Science Center Library at the University of Florida, Gainesville, Fla. Abstracts of all articles were reviewed for relevancy to the subject (DSF and ECK). Human case-control, cross-sectional, prospective, and descriptive studies presenting evidence of concomitant microvascular dysfunction of the heart and brain, heart and retina, heart and kidney, and heart and lung, were included. Postmortem/autopsy reports, and case reports were excluded. The search was updated on March 11, 2022, and no additional articles were identified.

### CLINICAL SIGNIFICANCE

- Microvascular dysfunction results in tissue damage and progressive organ failure.
- Unifying hypothesis suggests that microvascular dysfunction is a systemic illness.
- Uncovering shared pathologic mechanisms could inform new treatment strategies.

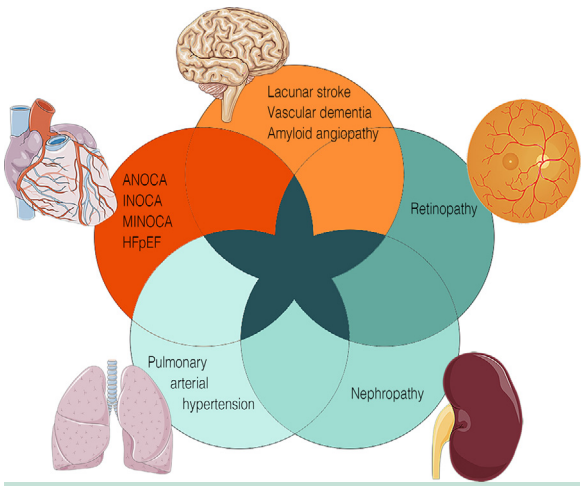


**Figure** Microvascular dysfunction affecting the heart, brain, retina, lung, and kidney, representing different manifestations of small vessel disease. They share pathophysiologic mechanisms and can occur concomitantly. ANOCA = angina with no obstructive coronary artery disease; HFpEF = heart failure with preserved ejection fraction; INOCA = ischemia with no obstructive coronary artery disease; MINOCA = myocardial infarction with no obstructive coronary arteries.

## CLINICAL MANIFESTATIONS OF MICROVASCULAR DYSFUNCTION OF THE HEART, BRAIN, KIDNEY, AND RETINA

The majority of patients undergoing coronary angiography for anginal symptoms do not have flow-limiting narrowing in their epicardial arteries,[7] and are diagnosed with angina with no obstructive coronary artery disease or ischemia with no obstructive coronary artery disease.[8] Coronary microvascular dysfunction is defined as limited coronary flow reserve or endothelial dysfunction that contributes to myocardial ischemia and angina in the absence of obstructive stenosis.[9] It is associated with increased morbidity and mortality, including myocardial infarction with no obstructive coronary arteries, and heart failure with preserved ejection fraction.[10]

Endothelial dysfunction, capillary rarefaction, microcirculatory plugging with microthrombi and microemboli, microvascular remodeling, and impaired autoregulation are key pathophysiologic mechanisms shared among microvascular dysfunction in different organs,[5,11] resulting in diverse presentations: Cerebral small vessel disease affects the microvasculature of the leptomeninges and the deep perforating branches of the anterior, middle, and posterior cerebral arteries.[12] This form of microvascular dysfunction manifests clinically as stroke, cognitive dysfunction, cerebral amyloid angiopathy, vascular dementia, depression, and anxiety.[13-16] It is the primary cause of lacunar stroke, and a contributing factor in up to 45% of cases of dementia.[4,13,14] Chronic kidney disease is a common condition affecting 20 million Americans.[17] Its pathophysiology is characterized by capillary bed destruction, deranged vasoreactivity, and fibrosis leading to progressive renal injury.[18] The retina is unique in that blood vessels can be directly visualized, allowing considerable insight into the pathophysiologic changes of the microvasculature. Intimal inflammation and fibrosis, edema, neovascularization, and

capillary degeneration result in retinopathy and associated vision loss.[19] Lastly, in the lungs, pulmonary arterial hypertension caused by vascular remodeling, vasoconstriction, and in situ thrombosis leads to increased pulmonary vascular resistance, progressive right heart failure, and death.[20]

## CONCOMITANT MICROVASCULAR DYSFUNCTION OF HEART AND BRAIN

Studies assessing concomitant microvascular dysfunction in the heart and brain are summarized in Table 1.[21-27] The largest is a descriptive analysis of 95 subjects with coronary microvascular dysfunction who underwent technetium-99m-hexamethyl-propylene-aminoxime brain single-photon emission computed tomography to assess for cerebral perfusion abnormalities.[21] The majority of subjects (76%) had evidence of abnormal cerebral perfusion. The relationship between brain and myocardial perfusion defects have been reported in smaller studies.[22,23] In one study of patients with slow coronary blood flow on coronary angiography, investigators reported decreased middle cerebral artery peak systolic, end diastolic, and mean flow velocities,[24] while in a smaller study no such association was found.[25] Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited cerebral small vessel disease linked to mutations in NOTCH3 in which patients present with stroke and dementia.[27] Two studies assessed concomitant heart involvement in CADASIL. In the first study, coronary flow reserve was found to be decreased in CADASIL patients

**Table 1** Evidence Supporting Common Pathophysiology Between Microvascular Dysfunction of the Heart and Brain

| Reference | Design | Objective | Population | n | Key Findings |
|---|---|---|---|---|---|
| Argirò et al 2021[26] | Descriptive | Determine prevalence and severity of CMD in patients with CADASIL | CADASIL | 32 | CFR and maximal MBF following regadenason infusion were decreased in CADASIL patients compared with controls. Degree of CMD did not correlate with extent of neurologic dysfunction. |
| Pai et al 2003[22] | Case-control | Assess brain findings in patients with CMD | CMD | 30 | High incidence of brain hypoperfusion lesions on Tc-99m-ECD brain SPECT, and coincident with myocardial defects on the thallium-201 myocardial perfusion SPECT |
| Brunelli et al 1996[25] | Descriptive | Measure cerebral blood flow and cerebrovascular vasodilator reserve in patients with CMD | CMD | 16 | Cerebral blood flow and cerebrovascular vasodilator reserve preserved in patients with CMD, not consistent with the hypothesis of a diffuse smooth−muscle disorder |
| Sun et al 2001[23] | Case-control | Assess brain findings in patients with CMD | CMD | 40 | 92% with definite myocardial perfusion defects on thallium−201 myocardial perfusion SPECT also had multiple hypoperfusion areas in the brain. Parietal lobes were the most common area of hypoperfusion, cerebellum was the least common |
| Karakaya et al 2011[24] | Cross-sectional | Investigate cerebral blood flow velocity in patients with slow coronary blood flow | Slow coronary blood flow | 32 | Right and left middle cerebral artery peak systolic, end diastolic and mean flow velocities were significantly lower in patients with slow coronary blood flow than those with normal coronary flow |
| Weidmann et al 1997[21] | Descriptive | Investigate cerebral blood flow in patients with CMD | CMD | 95 | 76% had pathologic findings suggestive of cerebral perfusion abnormalities |
| Lesnik Oberstein et al 2003[27] | Descriptive | Assess prevalence of myocardial ischemia in CADASIL | CADASIL | 63 | 25% of mutation carriers had ECG evidence of myocardial infarction vs none in the nonmutation carriers ($P = .011$). ECG changes pre-dated neurologic symptoms of CADASIL in all patients. |

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CFR = coronary flow reserve; CMD = coronary microvascular dysfunction; ECG = electrocardiogram; MBF = myocardial blood flow; MVD = microvascular dysfunction; SPECT = single-photon emission computed tomography.

compared with control subjects.[28] In the second study, 25% of CADASIL mutation carriers had evidence of myocardial infarction, whereas none of the nonmutation carriers had such findings.[26] Interestingly, the electrocardiographic changes in the CADASIL patients pre-dated the development of major neurologic symptoms.

## CONCOMITANT MICROVASCULAR DYSFUNCTION OF HEART AND KIDNEY

Some of the strongest evidence about the global nature of microvascular dysfunction is that of cardiovascular disease in patients with chronic kidney disease. While traditional risk factors are associated with both cardiovascular disease and chronic kidney disease, cardiovascular disease is more prevalent in patients with chronic kidney disease, even when adjusted for traditional risk factors.[29] Patients with chronic kidney disease are more likely to die from a cardiac event than from progression to end-stage renal disease.[30] In addition, kidney dysfunction is associated with increased risk of both acute and chronic forms of cerebral small vessel disease, including stroke and intracranial hemorrhage.[31]

While some functional or structural aspects of microvascular dysfunction can be directly assessed in the heart, retina, and brain, there is no widely accepted in vivo measurement of microvascular dysfunction in the kidney. However, peritubular capillary flow (renal plasma flow minus glomerular filtration rate) in humans,[32] and intravital microscopy in a murine sepsis model have been studied.[33] Studies reporting a correlation between microvascular dysfunction of the heart and kidney (Table 2[34-50]) relied on tests of kidney function, such as creatinine, glomerular filtration rate, and albuminuria to quantify renal microvascular dysfunction. Numerous studies have demonstrated that a lower glomerular filtration rate is related to decreased coronary flow reserve in the heart.[34-43] Similarly, 2 studies demonstrated an association between slow coronary contrast flow on coronary angiography and decreased glomerular filtration rate.[44,45] One study of 220 subjects with angina but no obstructive epicardial coronary artery disease reported creatinine clearance to be independently associated with the extent of microvascular dysfunction in the heart.[46] In hypertensive subjects, plasma levels of asymmetric dimethylarginine, a nitric oxide inhibitor, were highest in those with impaired glomerular filtration rate and coronary flow reserve in one study,[47] and in a separate study, those with an abnormal stress test but no significant epicardial coronary artery disease, low coronary flow reserve was associated with higher left ventricular mass index and albumin-to-creatinine ratio.[48] In a cross-sectional study, diabetics with renal insufficiency had reduced coronary flow velocity reserve compared with control subjects.[49] Lastly, in a cohort of women enrolled in the Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD) study, investigators found a significant inverse correlation between coronary blood flow (determined by invasive coronary function testing) and urine albumin-creatinine ratio, suggesting a systemic process involving both the heart and kidney.[50]

## CONCOMITANT MICROVASCULAR DYSFUNCTION OF HEART AND RETINA

Studies assessing the relationship between microvascular dysfunction of the heart and retina are summarized in Table 3.[51-57] In 2 studies, coronary reactivity testing was abnormal in diabetics with retinopathy.[51,52] In a descriptive study, 60 patients with microvascular dysfunction of the heart underwent optical coherence tomography to assess retinal abnormalities.[53] Superficial vascular density was abnormal in 45% of patients with microvascular dysfunction of the heart. Several studies have focused on retinal arteriolar caliber as a marker for microvascular dysfunction in the heart. For example, Wang et al[54] studied 212 subjects with no known cardiovascular disease and found that narrower retinal arterioles were associated with impaired hyperemic myocardial perfusion. In a separate study of patients with known coronary microvascular dysfunction, higher retinal arteriolar flow was seen in those with slow coronary artery blood flow.[55] These investigators concluded that the higher retinal arteriolar flow was likely a product of impaired vasodilation from microvascular dysfunction. Moreover, in a large cross-sectional study, women with small retinal venules were 3 times more likely to have microvascular angina compared with women with large retinal venules.[56] Finally, in a study of 4593 middle- and older-age adults with no known cardiovascular disease, the presence of narrow retinal arterioles was associated with left ventricular concentric remodeling independent of atherosclerotic burden.[57]

## CONCOMITANT MICROVASCULAR DYSFUNCTION OF HEART AND LUNG

Pulmonary hypertension, defined as resting mean pulmonary artery pressure measured by right heart catheterization ≥25 mm Hg, is further delineated into 5 groups, depending on the underlying pathophysiologic mechanism.[58] As it pertains to this review, group 1 pulmonary hypertension (pulmonary arterial hypertension) predominately affects the small resistance pulmonary arteries, is associated with a poor prognosis, and can be idiopathic, genetic, or associated with other conditions such as connective tissue diseases.[58,59] The concomitant occurrence of pulmonary hypertension and microvascular dysfunction of the heart has been described (Table 4[60-65]). In a study of patients with systemic sclerosis, investigators reported considerable overlap between cardiac involvement (both epicardial coronary artery disease and coronary microvascular dysfunction) and the presence of pulmonary hypertension.[60] For example, about a third of patients with pulmonary hypertension had severely reduced coronary flow reserve on invasive coronary reactivity testing. Other investigators report significantly lower myocardial perfusion on cardiac

**Table 2** Evidence Supporting Common Pathophysiology Between Microvascular Dysfunction of the Heart and Kidney

| Reference | Design | Objective | Population | n | Key Findings |
|---|---|---|---|---|---|
| Nelson et al 2019[34] | Cross-sectional | Measure CFR | ESRD on dialysis and non-obstructive CAD | 30 | CFR was reduced in patients with ESRD |
| Kashioulis et al 2020[35] | Cross-sectional | Identify abnormalities on echocardiography | Chronic kidney disease | 132 | Patients with CKD stages 3 and had left ventricular diastolic dysfunction and reduced CFR |
| Östlund-Papadogeorgos et al 2020[46] | Descriptive | Determine predictors of index of microvascular resistance | Chronic angina and non-obstructive LAD disease | 220 | Creatinine clearance was independently associated with index of microvascular resistance |
| Tsiachris et al 2012[48] | Descriptive study | Identify associations between CFR and cardiac and renal abnormalities | Untreated hypertensives with a positive stress test and no significant CAD | 37 | Never-treated hypertensives with low CFR had larger LV mass index and higher albumin to creatinine ratio compared with those with higher CFR |
| Mohandas et al 2015[36] | Descriptive study | Assess if eGFR is associated with reduced CFR | Women with signs/symptoms of ischemia referred for coronary angiography | 198 | eGFR significantly correlated with CFR |
| Bozbas et al 2008[37] | Cross-sectional study | Evaluate degree of CMD | ESRD on dialysis | 86 | CFR was impaired in ESRD compared with renal transplants and controls. On multivariate analysis, creatinine, age, and diastolic dysfunction correlated with CFR |
| Fukushima et al 2012[38] | Cross-sectional | Determine presence of impaired myocardial perfusion | Referred for myocardial perfusion PET scan without known CAD | 230 | Global MFR is reduced in patients with CKD and no regional perfusion deficits |
| Fujii et al 2008[47] | Cross-sectional | Identify relationship between ADMA, eGFR, and CMD | Hypertensives with normal or mild renal insufficiency | 66 | Plasma ADMA levels were highest in patients with reduced eGFR and CFVR<br>eGFR and CFVR were significantly associated with each other |
| Ragosta et al 2004[49] | Cross-sectional | Determine prevalence of impaired CVR in diabetics with nephropathy and angiographically normal coronary arteries | Diabetics with nephropathy but no CAD | 64 | Abnormal CVR was associated with patients who had diabetes and nephropathy but not in controls |
| Akin et al 2014[44] | Cross-sectional | Assess association between eGFR and coronary blood flow | Slow coronary blood flow without obstructive CAD and normal to mildly impaired renal function | 430 | eGFR was significantly correlated with SCF in patients with normal to mildly impaired renal function |
| Chade et al 2006[39] | Descriptive | Determine association between CKD and CMD | Patients referred for angiography where CAD was excluded | 605 | GFR was significantly associated with CFR Patients with impaired GFR were more likely to be older, hypertensive, and female |
| Sakamoto et al 2012[40] | Descriptive | Assess if impaired CFR is associated with CKD and cardio-cerebrovascular events | Patients with suspected CAD but no epicardial artery stenosis | 73 | Patients with CKD had a significantly lower CFR compared with those without CKD. In patients with low CFR, cardio-cerebrovascular events were more common compared with patients with normal CFR |

**Table 2** (*Continued*)

| Reference | Design | Objective | Population | n | Key Findings |
|---|---|---|---|---|---|
| Tsuda et al 2018[41] | Cross-sectional | Measure myocardial perfusion reserve | Chronic kidney disease | 92 | Patients with CKD had a significantly lower myocardial perfusion reserve compared with those without CKD |
| Bezante et al 2009[42] | Descriptive | Characterize changes in CFR and early renal disease | Hypertensives | 26 | Those with impaired CFR also had significantly lower eGFR |
| Imamura et al 2014[43] | Descriptive | Assess relationship between albuminuria and CMD | Chronic kidney disease | 175 | Worsening renal function was associated with lower CFVR. Albuminuria was the most powerful predictor of abnormal CFVR |
| Yilmaz and Yalta 2009[45] | Cross-sectional | Determine the presence of slow coronary flow in patients with impaired renal function | Patients with angiographically normal coronary arteries and a GFR <90 mL/min/1.73 $m^2$ | 207 | Those with impaired renal function had slower coronary flow (assessed by TIMI flow) compared with those with normal renal function |
| Jalnapurkar et al 2021[50] | Descriptive | Evaluate relationship between UACR and invasive coronary function testing | Women with INOCA enrolled in WISE-CVD | 152 | Coronary endothelial-dependent variables had significant inverse correlations with log UACR |

ADMA = asymmetric dimethylarginine; CAD = coronary artery disease; CFR = coronary flow reserve; CMD = coronary microvascular dysfunction; CFVR = coronary flow velocity reserve; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; INOCA = ischemia with no obstructive coronary artery disease; LV = left ventricular; MFR = myocardial flow reserve; MVD = microvascular dysfunction; SCF = slow coronary flow; TIMI = thrombolysis in myocardial infarction; UACR = urine albumin-creatinine ratio; WISE-CVD = Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction.

magnetic resonance testing in subjects with group 1 pulmonary hypertension compared with those without pulmonary hypertension, and the pulmonary artery pressure as an independent predictor of right and left ventricular myocardial perfusion.[61] Moreover, in a study of patients with hypertrophic cardiomyopathy, global myocardial flow reserve as measured by positron emission tomography was an independent predictor of concomitant pulmonary hypertension.[62] Lastly, studies by Raman et al[63-65] also report evidence of coronary microvascular dysfunction of the right and left ventricle on cardiac magnetic resonance testing in patients with pulmonary arterial hypertension.

## DISCUSSION

There is a significant body of information supporting the concept of microvascular dysfunction as a systemic and multi-organ pathologic process. A number of potential mechanisms have been proposed to explain these associations: In the heart and brain, microvascular dysfunction is associated with elevated serum levels of homocysteine, serotonin, asymmetric dimethylarginine, and uric acid, all of which perturb the nitric oxide pathway.[66-68] Bioavailable nitric oxide is also decreased in chronic kidney disease, which may contribute to both an increased risk of cardiovascular events and progressive renal dysfunction.[69] Additional evidence about systemic endothelial dysfunction comes from the Coronary Microvascular Angina (CorMicA) study, in which arterioles isolated from gluteal biopsies in patients with microvascular angina or variant angina exhibited reduced maximum relaxation with acetylcholine and increased sensitivity to vasoconstricting agents,[70] and the well-known multi-organ involvement seen in systemic sclerosis and systemic lupus erythematosus with abnormalities of the skin, lungs, kidney, heart, and gastrointestinal tract.[71] From the diagnostic perspective, investigators identified 16 circulating biomarkers that were found to be common to microvascular dysfunction of the heart, brain, and kidney in a meta-analysis.[68] These biomarkers represented multiple mechanistic pathways, including inflammation, coagulation/thrombosis, and endothelial dysfunction.

Two genetic illnesses, CADASIL and Fabry disease, may represent inherited forms of microvascular dysfunction. CADASIL, as discussed earlier, has been associated with impaired coronary flow reserve and maximal myocardial blood flow in 32 patients,[26] and also microvascular angina in several case reports.[72,73] Fabry disease, an X-linked lysosomal storage disease caused by a lack of alpha-galactosidase activity, results in the accumulation of globotriaosylceramide in cells and multi-organ failure.[74] This disease has been associated with microvascular angina[75] as well as cerebral small vessel disease.[76] In one study of 10 patients with Fabry disease and 24 controls, resting and hyperemic myocardial blood flow and coronary flow reserve assessed by positron emission tomography were significantly

**Table 3** Evidence Supporting Common Pathophysiology Between Microvascular Dysfunction of the Heart and Retina

| Reference | Design | Objective | Population | n | Key Findings |
|---|---|---|---|---|---|
| Akasaka et al, 1997[51] | Cross-sectional | Assess differences in CFR in patients with and without diabetes | CMD | 44 | CFR was reduced in patients with diabetes and diabetic retinopathy compared with controls. More severe retinopathy was associated with worse coronary flow reserve |
| Eslami et al, 2021[53] | Descriptive | Describe retinal changes in patients with CMD | CMD | 60 | Superficial vascular density was abnormal in ~ half of patients with CMD |
| Sundell et al, 2004[52] | Cross-sectional | Determine whether diabetic retinopathy is associated with reduced coronary vasoreactivity | Diabetic retinopathy | 33 | Dipyridamole-stimulated flow and coronary vascular resistance were blunted in diabetics with retinopathy compared with diabetics without retinopathy and controls |
| Liew et al, 2019[56] | Cross-sectional | Assess for differences in retinal microvasculature between patients with CMD and CAD | Patients with microvascular angina and CAD | 915 | Women (but not men) with small retinal venules were threefold more likely to have microvascular angina compared with women with large retinal venules |
| Arbel et al, 2014[55] | Cross-sectional | Determine utility of retinal blood flow as a predictor of slow coronary artery blood flow | CMD | 28 | Higher retinal arterial flow was observed in the slow coronary flow group |
| Wang et al, 2008[54] | Cross-sectional | Determine relationship between retinal arteriolar narrowing and myocardial perfusion in patients with and without CAD | Middle and older age adults with no known cardiovascular disease | 212 | Narrower retinal arterioles are associated with lower hyperemic myocardial perfusion in asymptomatic adults with no coronary calcification |
| Cheung et al, 2007[57] | Cross-sectional | Determine relationship between retinal arteriolar narrowing and left ventricular remodeling in patients with and without CAD | Middle and older age adults with no known cardiovascular disease | 4593 | Narrower retinal arterioles are associated with increased left ventricular concentric remodeling regardless of level of coronary atherosclerosis |

CAD = coronary artery disease; CFR = coronary flow reserve; CMD = coronary microvascular dysfunction; MVD = microvascular dysfunction.

**Table 4** Evidence Supporting Common Pathophysiology Between Microvascular Dysfunction of the Heart and Lungs

| Reference | Design | Objective | Population | n | Key Findings |
|---|---|---|---|---|---|
| Zhao et al, 2019[62] | Retrospective | Assess relationship between CMD and pulmonary HTN | HCM with and without pulmonary HTN | 89 | Global MFR measured by quantitative PET was an independent predictor for pulmonary HTN in patients with HCM |
| Vogel-Claussen et al 2011[61] | Prospective | Evaluate relationship between LV and RV perfusion with pulmonary hemodynamics | Known or suspected pulmonary HTN and controls | 41 | RV and LV vasoreactivity significantly reduced in subjects with pulmonary HTN Mean PA pressure was an independent predictor of RV and LV myocardial perfusion reserve index on CMR |
| Raman et al 2021[65] | Prospective | Assess prevalence of RV ischemia in pulmonary HTN without CAD | Pulmonary HTN and controls | 53 | Decreased OS-CMR in pulmonary HTN patients consistent with microvascular dysfunction of the RV |
| Raman et al 2020[64] | Prospective | Assess prevalence of LV ischemia in patients with pulmonary HTN | Pulmonary HTN, CAD, and controls | 47 | Decreased OS-CMR and T1 reactivity in pulmonary HTN patients without CAD consistent with microvascular dysfunction |
| Raman et al 2019[63] | Prospective | Determine feasibility of rest/stress OS-CMR in pulmonary HTN | Pulmonary HTN and controls | 29 | Compared with controls, patients with pulmonary HTN had myocardial deoxygenation of the inferior RV on OS-CMR<br>RV deoxygenation correlated with the presence of LV deoxygenation |
| Komocsi et al 2010[60] | Prospective | Investigate degree of overlap of CAD and pulmonary HTN in systemic sclerosis | Systemic sclerosis patients with suspected pulmonary HTN and suspected CAD | 30 | Angiographic coronary slow flow (quantified by TIMI frame count), was inversely related to CFR<br>Severely reduced CFR (measured invasively at time of coronary angiography) in 35% of patients with pulmonary HTN |

CAD = coronary artery disease; CFR = coronary flow reserve; CMD = coronary microvascular dysfunction; HCM = hypertrophic cardiomyopathy; HTN = hypertension; LV = left ventricle; MFR = myocardial flow reserve; MVD = microvascular dysfunction; OS-CMR = oxygen-sensitive cardiac magnetic resonance; PA = pulmonary artery; RV = right ventricle; TIMI = thrombolysis in myocardial infarction.

lower in patients with the disease vs reference subjects.[75] Interestingly, female heterozygote patients with Fabry disease are at increased risk of developing small vessel disease of the kidney, heart, and brain despite normal levels of alpha-galactosidase activity.[76]

We recognize several limitations in this review: First, we focused our review on study level data supporting concomitant microvascular dysfunction in the heart and another organ including the kidney, brain, retina, and lung. There are data supporting concomitant microvascular dysfunction in other combinations not including the heart (such as the brain/retina and the kidney).[77] Second, we only included full text articles in English, so this may not be a complete list of all available data.

In conclusion, the reported evidence that supports the intriguing notion that microvascular dysfunction is a global pathologic process was reviewed. We contend that the diagnosis of microvascular dysfunction affecting the heart, brain, kidney, lung, or retina should prompt evaluation of other possible affected organs. A number of knowledge gaps need to be addressed to better understand this ubiquitous process and its shared pathophysiology which will ultimately inform novel therapies.

## ACKNOWLEDGMENT

The authors would like to thank Hannah F. Norton (Associate University Librarian and Chair of the Health Science Center Library at the University of Florida, Gainesville, Florida) for her expertise regarding our literature search.

## References

1. Gutterman DD, Chabowski DS, Kadlec AO, et al. The human microcirculation. Regulation of flow and beyond. *Circ Res* 2016;118(1):157–72.
2. Thompson CS, Hakim AM. Living beyond our physiological means. Small vessel disease of the brain is an expression of a sytemic failure in arteriolar function: A unifying hypothesis. *Stroke* 2009;40(5):e322–30.
3. Sax FL, Cannon RO, Hanson C, Epstein SE. Impaired forearm vasodilator reserve in patients with microvascular angina. Evidence of a generalized disorder of vascular function? *N Engl J Med* 1987;317(22):1366–70.

4. Berry C, Sidik N, Pereira AC, et al. Small-vessel disease in the heart and brain: current knowledge, unmet therapeutic need, and future directions. *J Am Heart Assoc* 2019;8(3):e011104.
5. Mejia-Renteria H, Matias-Guiu JA, Lauri F, Yus M, Escaned J. Microcirculatory dysfunction in the heart and brain. *Minerva Cardioangiol* 2019;67(4):318–29.
6. Thomas MA, Hazany S, Ellingson BM, Hu P, Nguyen KL. Pathophysiology, classification, and MRI paralles in microvascular disease of the heart and brain. *Microcirculation* 2020;27(8):e12648.
7. Kunadian V, Chieffo A, Camici P, et al. An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology Working Group on coronary pathophysiology & microcirculation endorsed by Coronary Vasomotor Disorders International Study Group. *Eur Heart J* 2020;41(37):3504–20.
8. Murthy VL, Naya M, Taqueti VR, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 2014;129(24):2518–27.
9. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. *Circulation* 2017;135(11):1075–92.
10. DelBuono MG, Montone RA, Camilli M, et al. Coronary microvascular dysfunction across the spectrum of cardiovascular diseases. *J Am Coll Cardiol* 2021;78(13):1352–71.
11. Patel H, Aggarwal NT, Rao A, et al. Microvascular disease and small-vessel disease: the nexus of multiple diseases of women. *J Womens Health (Larchmt)* 2020;29(6):770–9.
12. Li Q, Yang Y, Reis C, et al. Cerebral small vessel disease. *Cell Transplant* 2018;27(12):1711–22.
13. Cannistraro RJ, Badi M, Eidelman BH, Dickson DW, Middlebrooks EH, Meschia JF. CNS small vessel disease: a clinical review. *Neurology* 2019;92(24):1146–56.
14. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;42(9):2672–713.
15. Fang Y, Qin T, Liu W, et al. Cerebral small-vessel disease and risk of incidence of depression: a meta-analysis of longitudinal cohort studies. *J Am Heart Assoc* 2020;9(15):e016512.
16. Gatti L, Tinelli F, Scelzo E, et al. Understanding the pathophysiology of cerebral amyloid angiopathy. *Int J Mol Sci* 2020;21(10):3435.
17. Drawz P, Rahman M. Chronic kidney disease. *Ann Intern Med* 2015;162(11):ITC1–16.
18. Krishnan S, Suarez-Martinez AD, Bagher P, et al. Microvascular dysfunction and kidney disease: challenges and opportunities? *Microcirculation* 2021;28(3):e12661.
19. Duh EJ, Sun JK, Stitt AW. Diabetic retinopathy: current understanding, mechanisms, and treatment strategies. *JCI Insight* 2017;2(14):e93751.
20. Lan NSH, Massam BD, Kulkarni SS, Lang CC. Pulmonary arterial hypertension: pathophysiology and treatment. *Diseases* 2018;6(2):38.
21. Weidmann B, Jansen WC, Bock A, Assheuer J, Tauchert MO. Technetium-99m-HMPAO brain SPECT in patients with syndrome X. *Am J Cardiol* 1997;79(7):959–61.
22. Pai PY, Liu FY, Kao A, Lin CC, Lee CC. A higher prevalence of abnormal regional cerebral blood flow in patients with syndrome X and abnormal myocardial perfusion. *Jpn Heart J* 2003;44(2):145–52.
23. Sun SS, Shiau YC, Tsai SC, Ho YJ, Wang JJ, Kao CH. Cerebral perfusion in patients with syndrome X: a single photon emission computed tomography study. *J* Neuroimaging 2001;11(2):148–52.
24. Karakaya O, Koçer A, Esen AM, Kargin R, Barutcu I. Impaired cerebral circulation in patients with slow coronary flow. *Tohoku J Exp Med* 2011;225(1):13–6.
25. Brunelli C, Nobili F, Spallarossa P, et al. Cerebral blood flow reserve in patients with syndrome X. *Coron Artery Dis* 1996;7(8):587–90.
26. Argirò A, Sciagrà R, Marchi A, et al. Coronary microvascular function is impaired in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Eur J Neurol* 2021;28(11):3809–13.
27. Lesnik Oberstein SA, Jukema JW, Van Duinen SG, et al. Myocardial infarction in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). *Medicine (Baltimore)* 2003;82(4):251–6.
28. Wang MM. CADASIL. *Handb Clin Neurol* 2018;148:733–43.
29. Weiner DE, Tighiouart H, Elsayed EF, et al. The Framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol* 2007;50(3):217–24.
30. Bajaj NS, Singh A, Zhou W, et al. Coronary microvascular dysfunction, left ventricular remodeling, and clinical outcomes in patients with chronic kidney impairment. *Circulation* 2020;141(1):21–33.
31. Marini S, Georgakis MK, Anderson CD. Interactions between kidney function and cerebrovascular disease: vessel pathology that fires together wires together. *Front Neurol* 2021;12:785273.
32. Futrakul N, Futrakul P. Renal microvascular disease predicts renal function in diabetes. *Ren Fail*. 2012;34(1):126-129.
33. Wu L, Gokden N, Mayeux PR. Evidence for the role of reactive nitrogrn species in polymicrobial sepsis-induced renal peritubular capillary dysfunction and tubular injury. *J Am Soc Nephrol* 2007;18(6):1807–15.
34. Nelson AJ, Dundon BK, Worthley SG, et al. End-stage renal failure is associated with impaired coronary microvascular function. *Coron Artery Dis* 2019;30(7):520–7.
35. Kashioulis P, Guron CW, Svensson MK, Hammarsten O, Saeed A, Guron G. Patients with moderate chronic kidney disease without heart disease have reduced coronary flow velocity reserve. *ESC Heart Fail* 2020;7(5):2797–806.
36. Mohandas R, Segal MS, Huo T, et al. Renal function and coronary microvascular dysfunction in women with symptoms/signs of ischemia. *PLoS One* 2015;10(5):e0125374.
37. Bozbas H, Pirat B, Demirtas S, et al. Evaluation of coronary microvascular function in patients with end-stage renal disease, and renal allograft recipients. *Atherosclerosis* 2009;202(2):498–504.
38. Fukushima K, Javadi MS, Higuchi T, 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* 2012;53(6):887–93.
39. Chade AR, Brosh D, Higano ST, Lennon RJ, Lerman LO, Lerman A. Mild renal insufficiency is associated with reduced coronary flow in patients with non-obstructive coronary artery disease. *Kidney Int* 2006;69(2):266–71.
40. Sakamoto N, Iwaya S, Owada T, et al. A reduction of coronary flow reserve is associated with chronic kidney disease and long-term cardiocerebrovascular events in patients with non-obstructive coronary artery disease and vasospasm. *Fukushima J Med Sci* 2012;58(2):136–43.
41. Tsuda N, Shiraishi S, Sakamoto F, et al. Quantification of myocardial perfusion reserve using dynamic SPECT images of patients with chronic kidney disease. *J Cardiol* 2018;71(2):174–80.
42. Bezante GP, Viazzi F, Leoncini G, et al. Coronary flow reserve is impaired in hypertensive patients with subclinical renal damage. *Am J Hypertens* 2009;22(2):191–6.
43. Imamura S, Hirata K, Orii M, et al. Relation of albuminuria to coronary microvascular function in patients with chronic kidney disease. *Am J Cardiol* 2014;113(5):779–85.
44. Akin F, Celik O, Altun I, Ayça B. Association of glomerular filtration rate with slow coronary flow in patients with normal to mildly impaired renal function. *Angiology* 2014;65(9):850.
45. Yilmaz MB, Yalta K. Coronary flow slows as renal function worsens. *Clin Cardiol* 2009;32(5):278–82.
46. Östlund-Papadogeorgos N, Ekenbäck C, Jokhaji F, et al. Blood haemoglobin, renal insufficiency, fractional flow reserve and plasma NT-proBNP is associated with index of microcirculatory resistance in chronic coronary syndrome. *Int J Cardiol* 2020;317:1–6.
47. Fujii H, Takiuchi S, Kawano Y, Fukagawa M. Putative role of asymmetric dimethylarginine in microvascular disease of kidney and heart in hypertensive patients. *Am J Hypertens* 2008;21(6):650–6.

48. Tsiachris D, Tsioufis C, Dimitriadis K, et al. Relation of impaired coronary microcirculation to increased urine albumin excretion in patients with systemic hypertension and no epicardial coronary arterial narrowing. *Am J Cardiol* 2012;109(7):1026–30.
49. Ragosta M, Samady H, Isaacs RB, Gimple LW, Sarembock IJ, Powers ER. Coronary flow reserve abnormalities in patients with diabetes mellitus who have end-stage renal disease and normal epicardial coronary arteries. *Am Heart J* 2004;147(6):1017–23.
50. Jalnapurkar S, Landes S, Wei J, et al. Coronary endothelial dysfunction appears to be a manifestation of a systemic process: a report from the Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD) study. *PLoS One* 2021;16(9):e0257184.
51. Akasaka T, Yoshida K, Hozumi T, et al. Retinopathy identifies marked restriction of coronary flow reserve in patients with diabetes mellitus. *J Am Coll Cardiol* 1997;30(4):935–41.
52. Sundell J, Janatuinen T, Rönnemaa T, et al. Diabetic background retinopathy is associated with impaired coronary vasoreactivity in people with Type 1 diabetes. *Diabetologia* 2004;47(4):725–31.
53. Eslami V, Mojahedin S, Nourinia R, Tabary M, Khaheshi I. Retinal changes in patients with angina pectoris and anginal equivalents: a study of patients with normal coronary angiography. *Rom J Intern Med* 2021;59(2):174–9.
54. Wang Y, Wong TY, Sharrett R, Klein R, Folsom AR, Jerosch-Herold M. Relationship between retinal arteriolar narrowing and myocardial perfusion. Multi-Ethnic Study of Atherosclerosis. *Hypertension* 2008;51:119–26.
55. Arbel Y, Sternfeld A, Barak A, et al. Inverse correlation between coronary and retinal blood flows in patients with normal coronary arteries and slow coronary blood flow. *Atherosclerosis* 2014;232(1):149–54.
56. Liew G, Mitchell P, Chiha J, et al. Retinal microvascular changes in microvascular angina: findings from the Australian Heart Eye Study. *Microcirculation* 2019;26(6):e12536.
57. Cheung N, Bluemke DA, Klein R, et al. Retinal arteriolar narrowing and left ventricular remodeling: the multi-ethnic study of atherosclerosis. *J Am Coll Cardiol* 2007;50(1):48–55.
58. Prins KW, Thenappan T. WHO group I pulmonary hypertension: epidemiology and pathophysiology. *Cardiol Clin* 2016;34(3):363–74.
59. Haque A, Kiely DG, Kovacs G, Thompson AAR, Condliffe R. Pulmonary hypertension phenotypes in patients with systemic sclerosis. *Eur Respir Rev* 2021;30(161):210053.
60. Komocsi A, Pinter T, Faludi R, et al. Overlap of coronary disease and pulmonary arterial hypertension in systemic sclerosis. *Ann Rheum Dis* 2010;69(1):202–5.
61. Vogel-Claussen J, Skrok J, Shehata ML, et al. Right and left ventricular myocardial perfusion reserves correlate with right ventricular function and pulmonary hemodynamics in patients with pulmonary arterial hypertension. *Radiology* 2011;258(1):119–27.
62. Zhao M, Liu M, Leal JP, et al. Association of PET-measured myocardial flow reserve with echocardiography-estimated pulmonary artery systolic pressure in patients with hypertrophic cardiomyopathy. *PLoS One* 2019;14(3):e0212573.
63. Raman KS, Stokes M, Walls A, et al. Feasibility of oxygen sensitive cardiac magnetic resonance of the right ventricle in pulmonary hypertension. *Cardiovasc Diagn Ther* 2019;9(5):502–12.
64. Raman KS, Shah R, Stokes M, et al. Left ventricular ischemia in precapillary pulmonary hypertension: a cardiovascular magnetic resonance study. *Cardiovasc Diagn Ther* 2020;10(5):1280–92.
65. Raman KS, Shad R, Stokes M, et al. Right ventricular myocardial deoxygenation in patients with pulmonary artery hypertension. *J Cardiovacs Magn Reson* 2021;23(1):22.
66. Ahmad A, Corban MT, Toya T, et al. Coronary microvascular endothelial dysfunction in patients with angina and nonobstructive coronary artery disease is associated with elevated serum homocysteine levels. *J Am Heart Assoc* 2020;9(19):e017746.
67. Odaka Y, Takahashi J, Tsuburaya R, et al. Plasma concentration of serotonin is a novel biomarker for coronary microvascular dysfunction in patients with suspected angina and unobstructive coronary arteries. *Eur Heart J* 2017;38(7):489–96.
68. Nowroozpoor A, Gutterman D, Safdar B. Is microvascular dysfunction a systemic disorder with common biomarkers found in the heart, brain, and kidneys? - A scoping review. *Microvasc Res* 2021;134:104123.
69. Baylis C. Nitric oxide deficiency in chronic kidney disease. *Am J Physiol Renal Physiol* 2008;294(1):F1–9.
70. Ford TJ, Rocchiccioli P, Good R, et al. Systemic microvascular dysfunction in microvascular and vasospastic angina. *Eur Heart J* 2018;39(46):4086–97.
71. Saygin D, Highland K, Tonelli AR. Microvascular involvement in systemic sclerosis and systemic lupus erythematosus. *Microcirculation* 2019;26(3):e12440.
72. Langer C, Adukauskaite A, Plank F, Feuchtner G, Cartes-Zumelzu F. Cerebral Autosomal Dominant Arteriopathy (CADASIL) with Cardiac Involvement (ANOCA) and subcortical leukencephalopathy. *J Cardiovasc Comput Tomogr* 2020;14(5):e1–6.
73. Rubin CB, Hahn V, Kobayashi T, Litwack A. A report of accelerated coronary artery disease associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Case Rep Cardiol* 2015;2015:167513.
74. Chan B, Adam DN. A review of Fabry disease. *Skin Therapy Lett* 2018;23(2):4–6.
75. Elliott PM, Kindler H, Shah JS, et al. Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with alpha galactosidase A. *Heart* 2006;92(3):357–60.
76. Søndergaard CB, Nielsen JE, Hansen CK, Christensen H. Hereditary cerebral small vessel disease and stroke. *Clin Neurol Neurosurg* 2017;155:45–57.
77. Toyoda K. Cerebral small vessel disease and chronic kidney disease. *J Stroke* 2015;17(1):31–7.