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Microvascular vasoregulatory dysfunction in African Americans - An enhanced opportunity for early prevention and treatment of atherosclerotic cardiovascular disease

Renee P. Bullock-Palmer [a,*], Panithaya Chareonthaitawee [b], Ervin Fox [c], Garth M. Beache [d]

[a] Department of Cardiology, Deborah Heart and Lung Center, Browns Mills NJ, Department of Medicine, Division of Cardiology, Thomas Jefferson University, Philadelphia, PA, United States of America
[b] Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, United States of America
[c] Division of Cardiology, Department of Medicine, University of Mississippi Medical Center, Jackson, MS, United States of America
[d] Department of Radiology, University of Louisville School of Medicine, Louisville, KY, United States of America

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ABSTRACT

Atherosclerotic cardiovascular disease and its risk factors and precursors are a major driver of disparities in cardiovascular health. This review examines reported evidence that vascular endothelial dysfunction, and its manifestation as coronary microvascular dysfunction, underlies observed excess morbidity and mortality in African Americans. Advanced imaging insights that reveal patho-mechanisms, along with population evidence from the Jackson Heart Study, and the growing evidence emanating from national and international clinical trials and registries are presented. We examine a physiological framework that recognizes insulin-resistant cardiometabolic underpinnings of the conditions of the American Heart Associations' Life's Essential Eight construct of cardiovascular health as a unifying basis that affords early prevention. Mechanistic-based therapeutic approaches, can subsequently be implemented to interrupt progression to adverse outcomes employing layered, or personalized, treatment strategies of a well-defined set of conditions or diseases. Remaining knowledge gaps are acknowledged.

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains the primary etiology of morbidity and mortality in adults in the United States (US), disproportionately impacting some populations, including African Americans (AA) [1]. Conditions that include hypertension, with and without myocardial hypertrophy, Type 2 diabetes mellitus (Type 2 DM), central obesity, dyslipidemia, and sleep apnea are highly prevalent risk factors or precursors of ASCVD in Black populations and are major drivers of health outcomes [2]. These conditions often occur as a cluster, highlighted by Reaven's classic research on the insulin cardiometabolic syndrome, and along with his observations on the impact of behaviors surrounding physical activity, nicotine, and diet, provides a physiological framework for the key metrics of the American Heart Association (AHA)'s Life's Essential 8 construct of cardiovascular health [3,4].

Advanced imaging permits quantitative estimation of the functional effects associated with the risk factors for ASCVD that reveals their patho-mechanisms. For example, in Type 2 DM and obesity, phosphorous-31 magnetic resonance (MR) spectroscopy, indexed using phosphocreatine and adenosine triphosphate (PCr/ATP) energetics, has documented metabolic evidence of ischemia [5,6]. In hypertension with hypertrophy (HTN-HYP), supply-demand balance status of critical oxygen (O_2) substrate, indexed using blood oxygenation level-dependent (BOLD) MR, has documented reduced vasodilator capacity, while oxygenation deficits have been documented in sleep apnea [7,8].

A unifying pathophysiology theme, encompassing the Coronary Vasomotor Disorders International Study (COVADIS) framework, implicates the vascular endothelium and has heightened recognition of the contribution of the microvasculature to adverse ASCVD outcomes, including ischemia and heart failure which disproportionately affect Black populations [9]. In this review, we explore a perspective to bend this curve. Since there is a cluster of ASCVD risk factors highly prevalent in Black populations, with putative mechanistic microvascular endothelial dysfunction, this provides an opportunity for prevention and

* Corresponding author.
E-mail address: renee.palmer@gmail.com (R.P. Bullock-Palmer).

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even at later stages may present therapeutic targets for disruption of progression to heart failure. This opportunity promises to afford improved cardiovascular outcomes in these patients.

2. Contribution of microvascular dysfunction to atherosclerotic cardiovascular disease

The microvascular endothelium has important homeostatic functions related to inflammation and to vasodilation [10,11]. Well documented evidence supports the relation of inflammation to microvascular disease, in the context of ASCVD co-morbidities, or risk factors [12].

Largely using positron emission tomography (PET) imaging, the relation of altered myocardial blood flow (MBF) and myocardial flow reserve (MFR) to biochemical markers of ischemic injury and heart failure, as evidenced by elevated high-sensitivity troponins and N-terminal pro brain natriuretic peptide, represents a major advance characterizing the vasodilator component of the pathophysiology of the endothelium in ASCVD [13]. The coronary vascular tree extends from the epicardial macro-vessels to the microvasculature. Catheter angiography interrogates anatomy ~0.2 mm, which is relevant to the observation that in a large national trial evaluating suspected coronary disease, macro-vessel assessment did not document a significant anatomic lesion in over half of participants [14]. To interrogate the microvasculature, a probe that is sensitive to processes at the micrometer level would be optimum.

BOLD MR was developed to visualize blood vessels in-vivo. The biophysical basis relies on the original observation by Linus Pauling that de-oxyhemoglobin, unlike oxyhemoglobin, is paramagnetic. This was initially developed as an in-vivo functional test of the oxygenation status of the brain, and subsequently explored to index epicardial coronary disease in humans [15]. The probed physiology takes place related to red blood cells at the mixed-venous, capillary level, ~ 8 μm, i.e., at a size-scale ~25 times smaller than that probed by catheter angiography. In the context of hypertensive hypertrophy without epicardial disease, it was specifically developed as an intramyocardial vasodilator functional test of the capacity to maintain O_2 homeostasis, indexing the supply-demand balance of critical O_2 substrate [7]. Mechanistic studies have related O_2 homeostasis to nitric oxide signaling affording enhanced therapeutic targeting [10].

We highlight a putative imaging mechanistic link relevant to ASCVD and its precursors and the progression to adverse outcomes, namely; an underlying oxygen homeostasis deficit, documented using the BOLD vasoregulatory functional test in HTN-HYP as a prototype condition of the insulin cardiometabolic syndrome, an ischemic energetic deficit observed in myocardial hypertrophy using PCr/ATP ratio, and evidence for a final common pathway of a derangement of predominantly diastolic vs systolic heart functioning in conditions manifesting heart failure with preserved ejection fraction (HFpEF), including myocardial hypertrophy. Although myocardial hypertrophy is a commonly implicated pathophysiology in these observations, the degree of its contribution has not been resolved [7,16,17,18]. Diastolic dysfunction can be indexed using transmitral-valve inflow E/A ratio, or alternatively mechanical function indices such as E/e', or diastolic/systolic strain or strain-rate [19]. As an expert technical note, global longitudinal strain (GLS) which is now a commonly reported mechanical function strain index, like EF characterization, essentially characterizes a systolic contractile measure. To more specifically reflect diastolic mechanics, MR strain and strain-rate literature support that an index such as the ratio of diastolic strain-rate/systolic strain-rate (obtainable as the magnitude of the respective peak slopes in early-diastole and in systole, derived from the strain contractile-function curve over the cardiac cycle), more adequately incorporates the contribution of diastolic function; because the deformation mechanics of early diastole relaxation can be as much as 30 % faster than systolic contraction, a value of this ratio of ~1.3 would be at the upper limits of normal, while a value that approaches 1, or that is <1 would be indicative of significantly reduced diastolic mechanical function [19]. Distinct characterization of diastolic vs systolic myocardial wall mechanics is of paramount importance for mechanism-guided therapies given that abnormal calcium signaling has been implicated in energetically-dependent diastolic dysfunction [10].

3. Prevalence, epidemiology and risk factors for microvascular vasoregulatory dysfunction

The prevalence of coronary microvascular dysfunction (CMD) is substantial with varying estimates often based on the definition, sample size, the population, and diagnostic approach [20]. Recently published studies reported prevalence rates from 26 % to 64 % [20]. Two recent studies are large investigations with over 1000 patients - one diagnosed CMD using PET-derived MFR < 2.0 and the other using coronary reactivity testing. These studies revealed prevalence rates of 53 % and 64 % respectively [20]. Despite the lower presence of epicardial coronary disease in women compared to men, these investigations showed similar prevalence rates of CMD for men and women [21].

However, prevalence rates in these studies have mostly come from patients being referred for coronary angiography based on chest symptoms and burden of atherosclerotic risk factors which may make them prone to selection bias and less likely to reflect true prevalence. A new ongoing study, Coronary Microvascular Function and CT Angiography (CorCTA) undertakes two objectives [22]. The first is to use a non-preselected population of patients with chest symptoms to diagnose CMD in all-comers (including those with chest symptoms but lower risk factor burden); this approach will provide more accurate population prevalence estimates. The second objective is to conduct a randomized clinical trial to investigate treatment strategies in CMD [22].

Risk factors for CMD are similar to standard risk factors for atherosclerotic disease including age, hypertension, diabetes, obesity, dyslipidemia, smoking, diet, and sleep disorders [23,24]. Often in AA these risk factors cluster resulting in an insulin-resistant, cardiometabolic syndrome [25–27]. Recent studies support the concept that coronary vasomotor dysfunction that is seen in CMD is a result of endothelial dysfunction and as a result is often associated with peripheral endothelial dysfunction and systemic microvascular disease (MVD) [28]. Cardiometabolic disorder is often associated with MVD which is a precursor to myocardial hypertrophy, congestive heart failure (CHF) with and without ischemic cause and ASCVD. Therefore, the benefit of better Life Simple 7/ Life Essential 8 scores being associated with lower incidence of CHF and ASCVD events in AA is perhaps partly secondary to the impact of a reduction in risk factor clustering which results in improved microvascular function [29,30]. Preliminary studies in the Jackson Heart Study have shown a strong relation between ideal cardiovascular health with Life Simple 7 or Life Essential 8 scoring and vascular function measures (aortic stiffness and endothelial function) in AA. In AA, MVD is associated with increased vascular pulsatility. and elevated aortic stiffness [31]. These hemodynamic effects may represent the mechanism through which MVD leads to end-organ damage (ASCVD and CHF) in this high-risk population [31]. MVD represents a potential preventive and therapeutic target for patients with cardiometabolic syndrome [24].

Other risk factors for MVD include systemic inflammation and myocardial diseases. Patients with systemic lupus erythematosus, rheumatoid arthritis, and other systemic inflammatory diseases are more likely to have MVD. Those with elevated C-reactive protein appear to have a higher prevalence of MVD further supporting the role of systemic inflammation. Systemic inflammation results from traditional risk factors such as those that cluster in cardiometabolic syndrome as well as autoimmune disease and other causes, and subsequently leads to microvascular dysfunction [32]. Further, patients with myocardial disease such as amyloidosis, myocarditis, dilated and hypertrophic cardiomyopathies and valvular heart disease (aortic stenosis) are at higher risk for CMD [33].

Genetic predisposition represents a potential confounding factor for

CMD. Fabry's disease and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) are genetic disorders with MVD that appear to involve multiple organs including the heart [34].

Endothelial dysfunction underlying CMD may be generalized to affect other tissues than the heart. There is evidence that MVD resulting from endothelial dysfunction is a systemic disease that involves multiple organs including the heart, brain, kidney, lung, and retina [34]. Those with MVD involving extracardiac organs are more likely to have CMD [34]. For example, those with MVD involving cerebral small arteries have lower coronary flow reserve (CFR). Individuals with MVD of the kidney with reduced glomerular filtration rate (GFR) and/or microalbuminuria were also found to have significantly lower CFR. The relation between kidney disease and CMD persisted after adjusting for confounding risk factors such as hypertension and diabetes.

4. Risk factor approach to clinical management of coronary microvascular dysfunction in ASCVD

We present an illustrative case of an African American patient with a cluster of risk factors, reviewed in the COVADIS framework [9]:

59-year-old African American female with a 20 pack-year history of tobacco smoking presented with suboptimally controlled hypertension, dyslipidemia, poorly controlled diabetes mellitus and a history of chest pressure and dyspnea brought on by physical exertion and mental stress. She also gives a history of insomnia and daytime somnolence. Body mass index (BMI) was 42, blood pressure 160/87 mmHg, low density lipoprotein (LDL) 165 mg/dl, and hemoglobin A1c of 8.6 %. Multiple prior tests included exercise stress myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT) which documented ischemic EKG changes with the occurrence of limiting chest pressure after 6 min of treadmill exercise at a peak heart rate of 160 bpm, but normal myocardial perfusion at subsequent imaging, and a normal left ventricular ejection fraction (LVEF) of 57 %. Ultimately invasive coronary angiography was performed documenting no significant obstructive coronary artery disease (CAD). Due to the persistence of her symptoms without evidence of obstructive CAD there was clinical suspicion for an etiology of CMD. Therefore she underwent stress MPI with positron emission tomography with hybrid CT imaging (PET-CT) which documented no coronary calcification, normal myocardial perfusion, and reduced MFR in all 3 coronary vessels [left anterior descending (LAD)- 1.31, left circumflex (LCx)- 1.25, right coronary artery (RCA)-1.43]. The global MFR was reduced at 1.33, diagnostic for the presence of coronary microvascular dysfunction. A transthoracic echocardiogram obtained due to her history of long-standing poorly controlled hypertension documented mild concentric left ventricular (LV) hypertrophy (wall thickness 11 mm), and no valvular heart disease, particularly aortic stenosis (AS), or asymmetric hypertrophy of the septum, in the expected most prevalent distribution of hypertrophic cardiomyopathy. LV systolic ventricular performance, as indexed by LVEF, was normal. Echo derived diastolic function, documented a mitral valve inflow velocity E/A ratio of 1.0 and septal and lateral e prime (e') of 5 cm/s and 9 cm/s respectively, left atrial volume index of 35 cc/m2, an average E/ e' ratio of 10 and no tricuspid regurgitation. These diastolic parameters suggested the presence of grade 1 LV diastolic dysfunction, characterized as impaired LV relaxation with normal LV filling pressures. LV global longitudinal strain (GLS), which effectively is a characterization of systolic wall deformation mechanics, was normal at −19.5 %. There were no reported symptoms of palpitations, or ECG findings to suggest atrial fibrillation.

Given the working diagnosis of CMD, instituted treatment included; aggressive risk factor behavioral-modification constituting smoking cessation, and weight loss activities of a heart healthy diet and increased physical activity via a home exercise program. Instituted pharmacotherapy consisted of an angiotensin converting enzyme inhibitor (ACEi), and amlodipine for hypertension, and isosorbide for angina. She was also placed on rosuvastatin for hyperlipidemia. Subspecialist referral included to a sleep specialist, with subsequent placement on continuous positive airway pressure (CPAP) therapy after documentation of obstructive sleep apnea (OSA). She was also referred to an endocrinologist for dedicated management of her type 2 DM. Approximately one year later, she remained free of tobacco smoking, BMI decreased to 30, blood pressure was improved at 127/73, LDL had decreased to 64, and HbA1c decreased to 6.9 %. The patient's angina symptoms were controlled, with no further episodes of worrisome chest pain or dyspnea.

Of special mention in this patient with echocardiographic features documenting LV diastolic dysfunction and increased LV wall thickness, given the mild degree of increased LV wall thickness as well as the normal LV filling pressures, amyloidosis was considered a less likely etiology for the increased LV wall thickness than hypertension, and specific work-up for amyloidosis was not done [35]. An important component of her therapeutic intervention was OSA therapy, given reported evidence of apparent beneficial effects of continuous positive airway pressure (CPAP) in aiding the management of some clustered risk factors of ASCVD, including difficult to control HTN, and also atrial fibrillation, probably related to its reported metabolic syndrome and endothelial function underpinnings [36–38]. Table 1 outlines patient's risk factors for ASCVD and objective features of CMD. Table 2 outlines the stratified therapeutic interventions implemented in the illustrative case presented.

The CORMICA trial documented that a multifaceted and stratified treatment approach can be effective in the management of CMD, albeit guided by detailed invasive diagnostic characterization in that study [39,40]. The current proposed early prevention and multi-tiered treatment approach is guided by more conventional clinical documentation of impaired coronary vasomotor function.

Relevant to this patient with obesity, documented by a BMI of 30, ongoing trials of agents such as sodium-glucose transport protein 2 (SGLT2) inhibitors [41], and glucagon-like peptide-1 (GLP-1) agonists [42,43], are been conducted which has therapeutic implications for obesity as a distinct component of the insulin-resistant cardiometabolic syndrome.

5. Conclusion

We have presented provocative mechanistic, population and clinical trial evidence for a risk factor framework for the development and progression to long-term adverse outcomes, including heart failure, in ASCVD, particularly in its manifestation as CMD. We have also illustrated an early prevention strategy (motivated by the AHA's Life's Essential 8 construct), combined with a tailored intervention approach based on the individuals' documented co-morbid conditions, to mitigate or interrupt the progression to long-term adverse outcomes, which is implementable at-scale. This advance may hold greatest promise in especially high-risk cohorts, including African Americans or Black populations, where there is an observed increased prevalence and clustering of risk factors. The paucity of data specific to African Americans in large clinical trials may warrant a call-to-action for augmented recruitment of such particularly high-risk groups in ongoing and planned clinical trials.

CRediT authorship contribution statement

Renee P. Bullock-Palmer: Writing – review & editing, Writing – original draft, Conceptualization.

Panithaya Chareonthaitawee: Writing – review & editing, Writing – original draft.

Ervin Fox: Writing – review & editing, Writing – original draft.

Garth M. Beache: Writing – review & editing, Writing – original draft, Conceptualization.

Renee P. Bullock-Palmer and **Garth M Beache** contributed equally to the manuscript. **Renee P. Bullock-Palmer** is responsible for all

Table 1
Summary of the Illustrative case outlining the patient's Risk Factors for (atherosclerotic cardiovascular disease) ASCVD and objective features that met COVADIS criteria for the diagnosis of coronary microvascular dysfunction [9,44].

Patient's Risk Factors for Atherosclerotic Cardiovascular Disease (ASCVD)
Hypertension with left ventricular hypertrophy
Type 2 Diabetes Mellitus
Obesity
Dyslipidemia
Obstructive Sleep Apnea
COVADIS Diagnostic Criteria for Coronary Microvascular Dysfunction (CMD) met by the Patient Presented
Angina symptoms of exertional chest pressure and dyspnea
Significant obstructive epicardial coronary artery disease excluded by invasive angiography
Impaired coronary microvascular function documented by quantitative positron emission tomography (PET)-indexed myocardial flow reserve (MFR)
Documentation of ischemic electrocardiogram (EKG) findings and chest pain with treadmill exercise

Table 2
An Outline of the Stratified Therapeutic Intervention Implemented in the Illustrative Case Presented.

Stratified Therapeutic Intervention Implemented in the Illustrative Patient
Behavior modification– smoking cessation, specific instructions for home-based exercise and heart healthy diet
Anti-thrombogenic therapy– Rosuvastatin was added to her existing low dose aspirin regimen
Control of Hypertension– An angiotensin converting enzyme inhibitor (ACEi) was chosen based on its documented additional beneficial effects on the renin-angiotensin and endothelin systems, and effects on ameliorating hypertrophy. Calcium antagonist, amlodipine, was also instituted based on consideration of documented diastolic dysfunction, with the aim to improve energetics-dependent calcium uptake and thus relaxation contractile function
Anti-anginal Therapy– Long-acting nitrate isosorbide was also added because of its beneficial effects on dyspnea and diastolic function
Multidisciplinary specialty care– Evaluation and management of sleep apnea, and intensive management of diabetes by endocrinologist

aspects of the manuscripts, and to whom all communications should be directed.

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.

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