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Editorial

End-organ ischemia in the absence of proximal obstructive arterial disease: Déjà vu or jamais vu?

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Chronic ischemia of a major end-organ, such as the heart or the brain, often arises from focal or diffuse atherosclerosis involving one or more arterial segments proximal to the under perfused territory. In such cases, focal lesions may be amenable to mechanical or surgical intervention and diffuse disease may be treated by a combination of medical and select interventional therapies. Alternatively, chronic end-organ ischemia can also occur in the absence of any proximal arterial obstruction. In such cases, when potentially reversible drivers of organ hypoperfusion have been excluded (e.g. dehydration, high output states), then a careful consideration of etiologies such as microvascular disease is warranted.

We and others have reported on microvascular dysfunction in the heart, whereby objective evidence of myocardial ischemia and even myocardial infarction can be present without any significant coronary artery stenoses on angiography, termed INOCA (ischemia with no obstructive coronary arteries) [1]. In this issue of *Atherosclerosis*, Ammirati and colleagues describe a similar phenomenon affecting the brain, whereby white matter hyperintense lesions (WMHL) on serial magnetic resonance imaging (MRI) were seen to progress in persons with non-obstructive carotid artery disease [2]. Common to both the heart and brain scenarios is the fact that these conditions appear to develop in the setting of traditional cardiovascular risk factors, such as hypercholesterolemia, but more frequently in women than in men. The overall non-classical presentation of end-organ ischemia in the absence of obstructive proximal arterial disease has led to these conditions being under-recognized, under-diagnosed, and generally not well understood.

Given the recent work by Ammirati and colleagues [2], we can begin to decipher where there may exist mechanistic commonalities across affected organ systems, including brain and heart. Using the same threshold of anatomic stenosis significance used for the coronary arteries, the investigators identified a group of 51 patients with non-obstructive carotid artery lesions, defined as a stenosis < 70% of the luminal diameter. In this study sample, a third of the patients had carotid lesions causing a 50–69% stenosis and the remainder had lesions with < 50% luminal diameter reduction. After a median follow up of 20 months, approximately half of these patients developed new WMHLs on brain MRI, most of which were on the same side as the moderate to minimal atherosclerotic changes seen in the carotid artery on ultrasound. Notably, progression of WMHLs was not associated with circulating levels of any particular lymphocyte or monocyte subpopulation, identified via cell surface markers, nor was it related to high-risk plaque features as determined by noninvasive ultrasound and computed tomography angiography. However, progressors were more likely to be women, have hypercholesterolemia, and have lower eGFR, similar to our findings in women with coronary microvascular dysfunction [3].

Although not directly assessed by the current study, these findings suggest that the most vulnerable patients could have concurrent cardiac, kidney, and other end-organ ischemia despite the presence of non-obstructive atherosclerosis involving proximal coronary, renal, or other large arteries (Fig. 1). Given the frequent co-occurrence of vascular disease across major organ systems, future investigations could expand to include assessment of end-organ ischemia and the extent of proximal atherosclerosis across multiple systems. Novel MRI and intracoronary imaging measurements of intraplaque hemorrhage, lipid-rich necrotic core, or thin-cap atheroma have been associated with increased risk of stroke and myocardial infarction in the absence of obstructive lesions [4–6], and may provide further insight into commonalities and differences of atherosclerotic processes in multiple organs.

If associated only partly to the presence of traditional atherosclerosis risk factors [3] and not related to variation in circulating cell subtypes, then some fundamental questions remain unanswered regarding the drivers of similar clinical phenomena affecting the arterial systems that perfuse vital organs. Perhaps a key pressing issue is the consistently observed predominance in women versus men. It is now well known that chronic myocardial ischemia, in the absence of obstructive coronary artery disease, is much more prevalent in women and associated with quantifiable coronary microvascular disease, as

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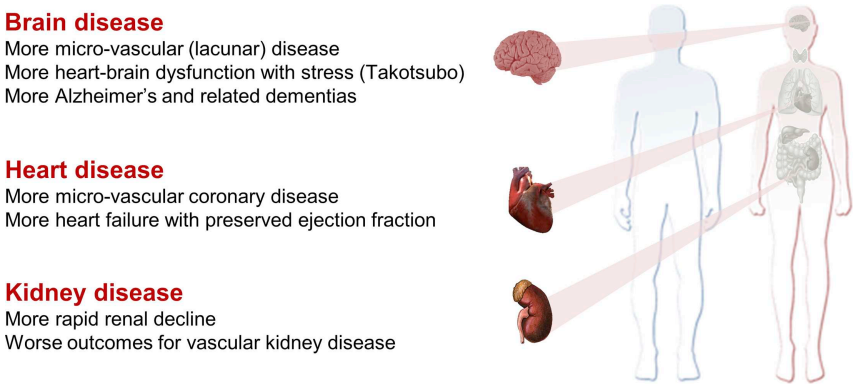

Fig. 1. Women compared to men tend to more frequently present with end-organ outcomes that have been associated with chronic ischemia in the absence of proximal artery occlusive disease.

well as adverse cardiac outcomes [7]. With respect to the brain, Ammirati and colleagues [2] have now reported a female predominance of progressive cerebral WMHLs, although the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort (RUN DMC) study did not find sex differences in the severity and progression of WHMLs in 276 patients over nine years [8]. It is possible that the female predominance is specific to the setting of microvascular disease in the absence of obstructive proximal arterial disease, and could be responsible for microinfarcts [9] and the known higher incidence of dementia in older women compared to older men [9,10]. With respect to the kidney, atherosclerotic renal artery stenosis is more common in men than in age-matched women [11], but in the absence of chronic kidney disease, decline in renal function is more rapid in older females than in older males for reasons that remain unclear [12]. When considering prior work done to investigate pathways leading to coronary microvascular dysfunction, and the putative mechanisms contributing to the formation of cerebral WMHLs, potential common factors include microvascular atherosclerosis, chronic inflammation, oxidative stress, endothelial dysfunction; all of these factors may or may not be hormone dependent.

Notwithstanding possible common pathophysiology, which will require substantial further investigations to unravel, the current report by Ammirati and colleagues [2] highlights the growing recognition of this particularly vulnerable patient population and the pressing need to determine the most appropriate approaches to their management in clinical practice. We have demonstrated in women with INOCA and MRI evidence of myocardial scar, that one-third did not carry a previously recognized diagnosis of myocardial infarction, suggesting that women with INOCA not uncommonly have a clinically underdiagnosed myocardial infarction [13]. Thus, there is a knowledge gap in recognition and diagnosis of this clinical syndrome. To help bridge this gap, the American Heart Association recently published a scientific statement on the diagnosis of myocardial infarction in the absence of obstructive coronary artery disease (MINOCA) [14]. The management of MINOCA and INOCA, however, is not well-established due to limited evidence-based literature, particularly a lack of prospective randomized controlled trials. Two randomized trials were recently launched to determine whether secondary preventive treatments that have been proven beneficial in patients with obstructive coronary artery disease also improve outcomes in patients with INOCA or MINOCA: 1) the WARRIOR clinical trial is underway to study intensive medical therapy of high intensity statin and maximally tolerated ACE inhibitors or angiotensin-receptor blockers (ARB) vs. usual care in 4422 symptomatic women with INOCA in the United States and will compare cardiovascular outcomes at 3 years (NCT03417388); 2) the international MINOCA-BAT clinical trial aims to randomize > 5600 MINOCA patients in a 2 × 2 factorial design to treatment with beta-blockers and ACEi/ARB versus matching placebo and will examine cardiovascular outcomes at 1 year (NCT03686696). Data are also emerging to understand the effects of similar therapy on WMHLs and cognitive function. In a recently published randomized clinical trial [15] using a 2 × 2 factorial design with an ARB (telmisartan vs placebo) and statin (rosuvastatin vs placebo) in older patients with hypertension, WMHLs progression and cognitive function decline were reduced in the statin group, and there was a beneficial synergistic interaction between rosuvastatin and telmisartan in this population. We look forward to more clinical trials to guide our understanding and treatment of patients with evidence of end-organ ischemia in the absence of proximal obstructive arterial disease.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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C. Noel Bairey Merz*
Barbra Streisand Women's Heart Center, Cedars-Sinai Smidt Heart Institute, Los Angeles, CA, USA
E-mail address: Noel.BaireyMerz@cshs.org.

Susan Cheng
Barbra Streisand Women's Heart Center, Cedars-Sinai Smidt Heart Institute, Los Angeles, CA, USA

Paolo Raggi
Division of Cardiology and Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada

Janet Wei
Barbra Streisand Women's Heart Center, Cedars-Sinai Smidt Heart Institute, Los Angeles, CA, USA

* Corresponding author. 127 S. San Vicente Blvd, Suite A3600, Los Angeles, CA, 90048, USA.