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COMMENT

Early detection of microvascular dysfunction in hypertension: the holy grail of cardiovascular prevention and risk assessment?

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The study of the structure and function of the microcirculation in hypertension has always fascinated the scientific community and currently remains a principal area of interest in hypertension. Arteries and arterioles with small diameters (diameters between 50 and 300 µm) are known to be the key determinants of both total peripheral resistance and organ perfusion, thus playing a critical role in determining blood pressure levels and their associated adverse consequences [1]. Retinal microvascular diameter, as a marker of peripheral resistance, has been widely investigated as a hypertension-related trait in previous studies [2–5]. However, the evaluation of the structural features of the microvasculature, such as the prognostically relevant wall-to-lumen ratio of subcutaneous small arteries, is restricted only to research settings due to its invasiveness. In recent years, increasing attention has been directed toward novel non-invasive indexes of microvascular structure and function (Table 1); however, for many of these, the clinical usefulness and prognostic implications are yet to be fully elucidated [6].

In the recent study of Junqueira C et al. [7], the authors offer a novel perspective to better understand some functional aspects of the microvasculature in hypertension by investigating novel microcirculatory parameters using nailfold videocapillaroscopy (NVC), a simple and relatively inexpensive technique that allows for the visualization of distal capillaries in the dermal papillae. First described by Raynaud in the XIX century, impaired architecture of the nail capillaries has been observed not only in the presence of autoimmune diseases, such as scleroderma, but also among hypertensive subjects, in whom an inverse association between the mean arterial pressure and capillary density was first described more than 25 years ago [8]. Digital technologies applied to NVC at high magnification (680×) now provide the opportunity to evaluate not only structural features but also the novel functional aspects of arteriolar and capillary networks, such as the mean and maximal width, the diameters of capillaries, and red blood cell velocity (RBCV) characteristics, both at baseline and after post-ischemic reperfusion.

The authors showed that patients with resistant hypertension (RH, $n = 25$) do not show significant differences in capillary ultrastructure (capillary density at baseline and after a post-occlusive stimulus or capillary diameters) compared to subjects with mild-to-moderate hypertension (MMH, $n = 25$) and normotensive subjects (NT, $n = 25$), but they present reduced baseline RBCV, lower maximal velocities after 1 min of arterial occlusion release (RBCVmax), and a longer reactive hyperemia response (TRBCVmax). Similar differences were found in uncontrolled hypertensive subjects compared with subjects with optimal blood pressure control. Intriguingly, in this context, the authors also found significantly higher C-reactive protein (CRP) levels, a marker of low-grade systemic inflammation, in RH subjects than those in MMH and NT subjects, although the potential association between RBCV and CRP levels was not tested in the present research.

Taken together, these results suggest that abnormalities in RBCV in RH and uncontrolled hypertension subjects can be detected at an early stage of microvascular damage where structural changes are not yet apparent. Moreover, in these subjects, an impaired flow profile at baseline and in response to an ischemic stimulus may reflect abnormal vasoconstrictor tone and may ultimately suggest the presence of endothelial dysfunction. Finally, the evidence of increased CRP levels in RH subjects may link microcirculatory dysfunction, low-grade systemic inflammation, and endothelial dysfunction.

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Table 1 Main characteristics of indexes of microvascular structure and function

Index	Brief descrpition	Clinical meaning	Prognostic implications
Media-to-lumen ratio of subcutaneous small arteries	Obtained by pressure and wire micromyography, very accurate and reproducible. Usually obtained by biopsy of subcutaneous fat or during surgical procedure	Associated with similar alterations of the microvasculature in other organs	Independent predictor of cardiovascular events in hypertension (especially hypertrophic remodeling)
Microvascular rarefaction	Number or small vessels in a given volume of tissue. Flow reserve (number of recruited vessels after hyperemic stimulus) could be non-invasively evaluated by videomicroscopy	Microvascular rarefaction is reduced in essential hypertension. Flow reserve is inversely associated with systolic blood pressure	Reduced coronary flow reserve predicts cardiovascular events. Microvascular rarefaction is associated to media-to-lumen ratio
Retinal arteriolar-to-venular ratio	Ratio between arteriolar and venular external diameters, automatically evaluated by computerized ophtalmoscopy	Associated with other markers of target organ damage (e.g., white matter lesions)	Predictor of cardiovascular events in women (not in men)
Wall thickness/internal lumen ratio of retinal arteriolae	Evaluated by scanning laser ophtalmoscopy coupled with laser Doppler technique for the evaluation of internal diameter. Adaptative optics imaging systems allows direct visualization of the retinal arterial wall	Associated with media-to-lumen ratio of subcutaneous small arteries. Associated with carotid intima-media thickness and microalbuminuria	To be demonstrated (subjects with previous cerebrovascular events showed increased ratio as compared to controls)

Compared to endothelial dysfunction in physiological aging, hypertensive subjects are known to exhibit early impaired nitric oxide availability [9]. However, the first step in the initiation of the development of microcirculatory dysfunction requires further clarification. Genetic, epigenetic, inflammatory, and stochastic factors leading to microvascular damage may all be good candidates [10]. Accordingly, relevant fibrosis has recently been shown in low-resistance arteries of patients with essential hypertension, elevated fibronectin, and TGF-β1 contents, and decreased laminin and emilin-1 contents in the tunica media [11]. In the present study, a sub-analysis conducted on subjects not taking statins showed an increase in endothelin levels among RH and MMH individuals, which may be consistent with the above hypothesis since fibrosis is associated with elevated endothelin expression by smooth muscle cells, fibroblasts, and vascular endothelial cells [12]. Intestinal dysbiosis may also be involved in promoting microvascular damage as accumulating evidence suggests a possible role of lipopolysaccharide-induced endothelial cell damage [13], although this rather speculative hypothesis should be further investigated in the future.

The study of Junqueira C et al. may stimulate future research on early detection of microvascular dysfunction in hypertension and other clinical settings by evaluating RBCV profiles using NVC. Appropriately sized and methodologically sound studies should also be performed to overcome the main limitations that currently restrict the generalizability of the results from the present study. Above all, possible confounding effects on the overall results for antihypertensive drugs with associated vasodilatory properties, such as vasodilating β-blockers or dihydropyridine calcium channel blockers, should be appropriately addressed. Another important aspect warranting investigation is related to the potential effect of blood hematocrit, which is influenced by sex and volume status, on red blood cell velocities.

Well-designed and controlled studies are needed to better clarify the main determinants of RBCV and microcirculatory "responses" to ischemia, the effects of different anti-hypertensive agent combinations, and the potential clinical and prognostic impact of these novel measures of microvascular function in essential and RH.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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