

Review

# Microcirculation in Hypertension: A Therapeutic Target To Prevent Cardiovascular Disease?

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**Abstract:** Arterial hypertension is a common condition worldwide and an important risk factor for cardio- and cerebrovascular events, renal diseases as well as microvascular eye diseases. Established hypertension leads to chronic vasoconstriction of small arteries as well as to decreased lumen diameter and thickening of the arterial media or wall with a consequent increased media-to-lumen ratio (MLR) or wall-to-lumen ratio (WLR). This process, defined as vascular remodeling, was firstly demonstrated in small resistance arteries isolated from subcutaneous biopsies and measured by micromyography, and this is still considered the gold-standard method for the assessment of structural alteration in small resistance arteries; however microvascular remodeling seems to represent a generalized phenomenon. An increased MLR may impair organ flow reserve, playing a crucial role in the maintenance and, probably, also in the progressive worsening of hypertensive disease, as well as in the development of hypertension-mediated organ damage and related cardiovascular events, thus possessing a relevant prognostic relevance. New, non-invasive techniques, such as Scanning Laser Doppler Flowmetry or Adaptive Optics, are presently under development, focusing mainly on the evaluation of WLR in retinal arterioles; recently, also retinal microvascular WLR was demonstrated to have a prognostic impact in term of cardio- and cerebrovascular events. A rarefaction of capillary network has also been reported in hypertension which may contribute to flow reduction and impairment in oxygen delivery to different tissues. These microvascular alterations seem to represent an early step in hypertension-mediated organ damage since they might concur to microvascular angina, stroke, and renal dysfunction. In addition, they could be a marker useful in monitoring the beneficial effect of antihypertensive treatment. Also conductance arteries may be affected by a remodeling process in hypertension, and an interrelationship is present structural changes in the small and large, conductance arteries. The review will address the possible relations between structural microvascular alterations and hypertension-mediated organ damage and their potential improvement with antihypertensive treatment.

**Keywords:** microcirculation; peripheral circulation; remodelling; small resistance arteries; vascular biology

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## INTRODUCTION

Cardiovascular diseases are the main cause of death worldwide, resulting in around 18 million deaths per year (WHO, 2020) (1), and hypertension is considered as the main contributor to such a global burden (2). Effective blood pressure (BP) control is a mandatory factor in order to improve hypertensive target organ damage and subsequent cardiovascular morbidity and mortality (2).

Functional, mechanical and structural alterations of the microvasculature may be observed in patients with essential hypertension even at very early stages (3-5) and contribute to the development of hypertension complications and cardiovascular prognosis (3,5).

In particular, in this setting, microvascular remodeling is a key event in triggering cardiovascular diseases (6,7).

The molecular mechanisms underlying the development of vascular remodeling are only partly understood. However, among the factors that may contribute to microvascular changes, an important role may be played by vascular inflammation with infiltration of inflammatory circulating cells and release of inflammatory cytokines and chemokines, proliferative growth factors, as well as oxidative stress related to both a reduction in nitric oxide bioavailability and increased reaction oxygen species production (5,8,9). These changes are promoted by mechanical, hemodynamic or metabolic vascular insult and result in altered vascular smooth muscle cell phenotype and accumulation of extracellular matrix (9). The present review briefly summarizes current knowledge about microvascular remodeling and its role in hypertension-mediated organ damage and consequent cardiovascular events.

### MICROVASCULAR REMODELING IN HYPERTENSION

Cardiovascular and metabolic diseases (in particular arterial hypertension), are very commonly associated with alterations in microcirculation (4,6,7); morphological changes may involve small resistance arteries, arterioles, capillaries and post-capillary venules (3,6,10). BP is mainly influenced by vessels resistance and microcirculation is the key element of peripheral resistance regulation. As mentioned, the microcirculation may be subdivided in small arteries, arterioles and capillaries. Small resistance arteries are defined as arteries with a lumen diameter roughly between 350 and 100  $\mu\text{m}$ . Their structure consists in an outer connective tissue adventitia, a smooth muscle cells tunica media and the endothelial layer (5,6). Arterioles are vessels with internal diameter below 100  $\mu\text{m}$ , characterized by a single layer of smooth muscle cells. Small arteries and arterioles account for 45- 50% of peripheral resistance and are defined as resistance arteries. These vessels have the capacity of contracting when transmural pressure increases, a feature called myogenic tone. A 23-30 % of peripheral resistance is to be ascribed to capillaries (internal diameter below 7  $\mu\text{m}$ ), whose wall is constituted only by a monolayer of endothelial cells (5,6).

It was proposed several years ago that increases systemic vascular resistance may be a consequence of vascular smooth muscle increase and concomitant narrowing of the arteriolar lumen (3,4,6,7,11). Microcirculation remodeling takes place in primary hypertension (6,10). Remodeling may be classified according to lumen and wall cross sectional area changes (12,13). Hence, remodeling might be inward when internal diameter is reduced and outward when lumen is unchanged (12,13). On the other hand, hypertrophic remodeling occurs when the vessel wall material, i.e. media/wall cross-sectional area, increases along with media/wall thickness whereas if media/wall cross-sectional area does not change or is reduced then remodeling is defined eutrophic or hypotrophic, respectively (12,13). Inward eutrophic remodeling is mainly observed in primary hypertension with media thickness increase and lumen diameter decrease resulting in unchanged media-cross sectional area (11-14). On the contrary, hypertrophic remodeling, which may be outward or inward, it has been shown in secondary form of hypertension (14), and in cardiovascular diseases as diabetes mellitus (15,16) and obesity (17,18) and metabolic syndrome (19), as well as in other endocrine diseases (20,21), independently on the presence of an increase in BP increase. As result of a remodeling process the wall to lumen ratio (WLR) and media to lumen ratio (MLR), defined as the ratio between wall and media thickness respectively and lumen diameter, increase.

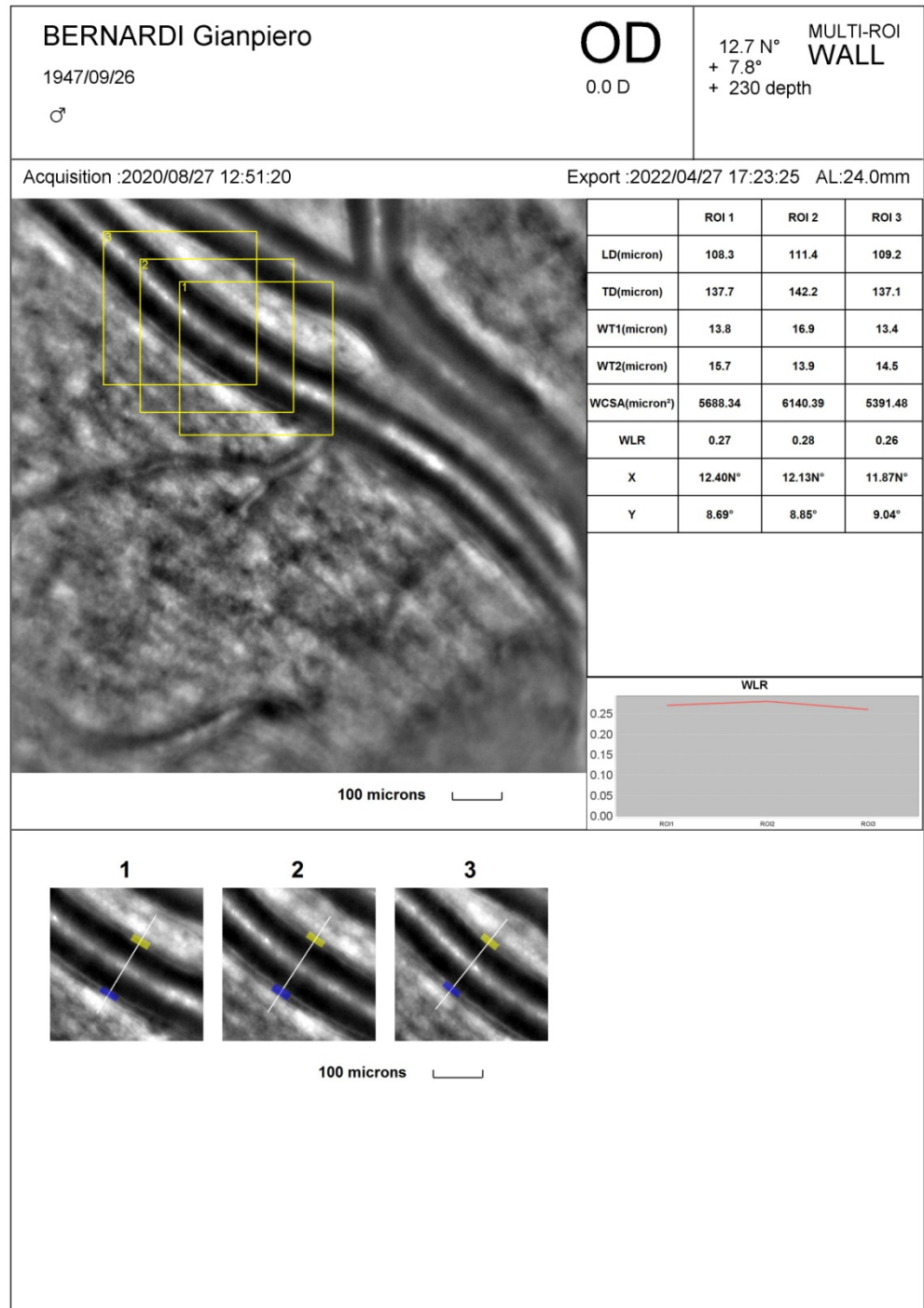
Hypertensive patients (4,11) (but also obese (22) or diabetic patients (4) present reduced basal and total capillary density compared to normotensive controls showing a structural anatomical rarefaction of capillaries rather than the presence of non-perfused vessels (4). This reduction in total capillary density may consequently lead to an increase in peripheral resistances thus negatively affecting tissue perfusion and nutrient delivery (23).

The time-course of the development of hypertension in respect with the onset of microvascular alterations is not clear. An increase in the MLR of mesenteric small resistance arteries of spontaneously hypertensive rats may be present in a pre-hypertensive phase (4). Data in humans are obviously difficult to obtain, since very few longitudinal data are presently available (4).

As previously mentioned, the hallmark of a microvascular remodeling process is an increased WLR and/or MLR. These parameters were initially measured in small resistance arteries by using wire or pressure micromyography, an *in vitro ex vivo* technique in which a small artery is isolated from subcutaneous fat tissue and mounted on wire or glass cannulas and studied in isometric or isobaric condition (24-26). Nowadays, non-invasive techniques have become available (27) such as Scanning Laser Doppler Flowmetry and Adaptive Optics (AO) which allow an accurate visualization and measurement of retinal vessel morphological parameters at high resolution providing similar information compared to the micromyographic system (28). In particular, Scanning Laser Doppler Flowmetry allows to measure the external diameter of retinal arterioles in reflection images and to evaluate the internal diameter in perfusion images according to a laser Doppler technique then providing an automatic estimation of WLR (29,30). With Adaptive Optics internal and external diameter of retinal arterioles are derived through an algorithm detecting the gradient of light's reflection between the lumen of the vessel and the wall; these data are then used to calculate WLR and wall cross-sectional area (27,31) (Figure 1). Compared to Scanning Laser Doppler Flowmeter, Adaptive Optics detects retinal arterioles remodeling with a lower intra-observer variability (28) and provides very high quality images (31) (Figure 1).

Cost, advantages, disadvantages, and indications/perspectives of the different available techniques for a non-invasive investigation of microvascular structure are summarized in Figure 2 (27).

**Figure 1.** Evaluation of the morphology of retinal arteries by adaptive optics. Example of images obtained with adaptive optics (AO camera, Rtx-1, Imagine Eyes, Orsay, France) (left and bottom) and measurement of morphological parameters using a dedicated software (right). From reference 4.



**Figure 2.** Cost, advantages, disadvantages, and indications/perspectives of the available techniques for a non-invasive investigation of microvascular structure. From reference 27.

Technique	Cost (\$)	Advantages	Disadvantages	Indications/perspectives
Forearm plethysmography	1500–2000	Relatively inexpensive	Locally invasive, needs experience	Research purposes, not for extensive clinical use
Intravital microscopy/gly-cocalyx	3000–5000	Noninvasive	No prognostic data	Research purposes, not for extensive clinical use, though adoption in specific settings (ie, critical care) is being proposed
Naifold videocapillaroscopy	10.000–20.000	Noninvasive	No prognostic data	Research purposes in the cardiovascular setting, commonly used in rheumatology. Possible future demonstration of prognostic usefulness of such an approach might extend its clinical application to patients at elevated cardiovascular risk.
SLDF (Heidelberg Retina Flowmeter)	30.000–40.000	Some prognostic data available/possibility to assess endothelial function	No more in the market	Research purposes; potential for an extensive future clinical application in the cardiovascular field if technically developed by the producer
AO cameras	130.000–160.000	Reliable/possibility to assess endothelial function	Cost, no prognostic data	Commonly used in ophthalmology for specific clinical purposes. Potential for an extensive future clinical application in the cardiovascular field
Dynamic vessel analyzer (AV ratio)	50.000–60.000	Some prognostic data, relatively easy to perform	Cost, some limitations in reliability	Commonly used in ophthalmology for specific purposes
OCTA	20.000–70.000	Useful vascular information on choroidal microvessels in hypertensive patients, plenty of data provided	Imaging artifacts, high acquisition costs, role in the cardiovascular field still under evaluation	Commonly used in ophthalmology for specific purposes
Techniques for the evaluation of topological changes in the retinal vascular architecture or fractal dimensions	30.000–50.000	Some prognostic data (fractal dimensions)	Not standardized	Only research purposes
EndoPAT	2500–4000	Easy to perform, cost	Limited reliability	Only research purposes
Laser doppler flowmetry (skin)	1500–20.000	Easy to perform, cost	Limited reliability	Only research purposes

The costs reported are only broadly indicative, largely depending on the specific device and provider. AO indicates adaptive optics; OCTA, optical coherence tomography angiography; and SLDF, scanning laser doppler flowmetry.

### Prognostic role of microvascular structural alterations

MLR of subcutaneous small resistance arteries has been suggested to represent the most prevalent and earliest form of arterial damage in essential hypertension (32) and it may be present very early, even in prehypertensive phase at least in experimental model (4).

From a physiological point of view, the reduction of small artery and arteriole lumen is associated to an increase of flow resistance even in condition of maximal dilatation hence impairing the organ flow reserve (33–35). Indeed, a relationship between vasodilating capacity of coronary microcirculation and media to lumen ratio of subcutaneous small arteries was previously demonstrated (36) in patients with mild to moderate hypertension thus suggesting that structural alterations in the subcutaneous vascular district (evaluated by wire micromyography in isolated vessels from fat biopsies taken in the gluteal region) may be representative of similar alterations in coronary microcirculation, leading to a reduced coronary flow reserve (36,37).

Increase MLR of subcutaneous small resistance arteries has been positively related to hypertensive target organ damage such as left ventricular hypertrophy (38,39) or carotid artery structure (39)

Importantly, the changes in small artery structure have a prognostic significance in both primary and secondary hypertension and in type 2 diabetes; indeed, an increased MLR is associated with a reduced event-free survival for cardiovascular events in high risk patients (3,40) as well as in medium risk ones (3,41,42). Moreover, the presence of hypertrophic remodeling seems to be associated to an even worse prognosis compared to eutrophic remodeling (43,44). More details about the prognostic role of structural alterations in subcutaneous small resistance arteries evaluated by micromyography are reported in Reference 3.



On the other hand, WLR evaluated by Scanning Laser Doppler Flowmetry was proved to increase in patients with hypertension and cerebrovascular disease (29) and to directly be associated with urinary albumin excretion (45). Likewise, an increased WLR evaluated with Adaptive Optics correlated with age (46,47), BP (31) and may be improved by reduction of BP values by hypertensive treatment (46). Most recently, a prognostic role of WLR evaluated with AO was demonstrated (48). The event-free survival was significantly worse in 230 normotensive subjects and hypertensive patients with a baseline WLR above the median value of the population (0.28) according to Kaplan-Mayer survival curves and multivariate analysis (Cox's proportional hazard model) (48). The evidence was confirmed after restricting the analysis to cardiovascular events, excluding deaths and neoplastic diseases (48). Therefore, structural alterations of retinal arterioles evaluated by adaptive optics may predict total and cardiovascular events (48).

Most recently, it was also demonstrated that patients with coronary microvascular dysfunction, defined as the presence of a reduced myocardial flow reserve ( $\leq 2$ ), evaluated by Dynamic Single-Photon Emission Computed Tomography (SPECT), had higher rates of adverse outcomes than those without it (49).

However, it is not presently known whether capillary rarefaction may be related to cardiovascular events (3,4).

### **Possible prevention/regression of microvascular remodeling**

The next question to be answered is whether we should aim at correcting the structure of resistance vessels in the treatment of hypertension and whether this could affect the prognosis. Indeed, several drugs have been demonstrated to improve microvascular structure and therefore reduce MLR such as drugs inhibiting the renin-angiotensin-aldosterone system and dihydropyridinic calcium channel blockers whereas diuretic and beta-blocked do not seem to have any relevant effect (5,7,50).

There is clear evidence that angiotensin-converting enzyme (ACE)-inhibitors and angiotensin-receptor blockers (ARB) appear to be more effective than atenolol in terms of microvascular protection also in patients with diabetes mellitus (51-54). Along this line, the direct renin inhibitor aliskiren improved microvascular structural alterations to a similar extent, compared with ramipril, in mild hypertensive patients with type 2 diabetes mellitus (54).

An improvement of microvascular remodeling was also demonstrated in the retinal vasculature. In patients with hypertension aliskiren plus valsartan ameliorated the WLR of retinal arterioles measured non-invasively by Scanning Laser Doppler (55). The combination of lercanidipine and enalapril was more effective in reducing the retinal arteriole WLR compared to the combination of lercanidipine and hydrochlorothiazide (56). Using Adaptive Optics a normalization of retinal arteriole structure, was observed after chronic and effective antihypertensive treatment (46). In the contrary, a short-term reduction of blood pressure led only to an increase in the internal diameter of retina arterioles with no change in wall thickness or wall cross-sectional area (46).

A complete regression of the remodeling process is difficult to be obtained in patients with hypertension-mediated organ damage (i.e. left ventricular hypertrophy) or when comorbidities such as diabetes mellitus are present (3,4,7,50). Usually, in such clinical situations, an improvement, but not a full normalization of the MLR of subcutaneous small resistance arteries has been observed, despite effective BP reduction.

Several specific mechanisms may contribute to the beneficial effects of some drugs on small artery structure and on outcome, compared with other pharmacological strategies. Buus NH et al. observed that, in essential hypertension, after one year of treatment with the ACE-inhibitor perindopril coronary flow reserve improved with normalization of small subcutaneous arteries structure (57). In this study, the parallel group treated with the beta-blocker atenolol coronary flow worsened and small subcutaneous artery structure remained unchanged, despite a similar reduction in BP (57). Therefore, it could be speculated that the beneficial effect on hypertensive target organ damage of these drugs

may be due also to their ability in improving microvascular structure. Buus NH et al. (58) demonstrated also that MLR represents an independent predictor of cardiovascular events, beyond the extent of blood pressure reduction, in a cohort of moderate-risk essential hypertensive patients including not only untreated patients but also hypertensive patients during long-term effective treatment. This suggests that assessment of microvascular structure may also be important in treated patients, since it may allow to identify those who may benefit from a more aggressive treatment and further risk reduction.

In addition, since vascular damage in hypertension is caused also by the inflammation, oxidative stress and immune system activation, drugs selectively modulating these pathways could represent a potential and interesting strategy of treatment in the near future.

In patients with Conn's syndrome (primary aldosteronism due to an adenoma of the adrenals), the presence of a marked or persistent vascular remodelling, as indicated by a greater MLR of subcutaneous small resistance arteries was associated with lower chances of blood pressure normalization at long-term follow-up after adrenalectomy. Thus, the severity of structural alterations in subcutaneous small resistance arteries might predict the clinical outcome in these patients with secondary hypertension (59). Therefore, structural alterations of small arteries could possibly be considered an important intermediate endpoint for the evaluation of the efficacy of antihypertensive treatment (4).

Antihypertensive treatment with ACE inhibitors seem to improve capillary rarefaction (56,60), although some methodological caveats were raised (61); in any case it is not yet established whether a reversal of capillary rarefaction is associated with an improved prognosis (4).

#### **INTERRELATIONSHIPS BETWEEN MICROVASCULAR AND MACROVASCULAR REMODELING**

The large arteries are not only the target of high BP, but a determining factor in the pathogenesis of hypertension, particularly of isolated systolic hypertension and the increase in pulse pressure typical of aging (62,63). The large elastic arteries allow the conduction of blood from the heart to the resistance arteries but also the transformation of the pulsatile flow, generated by cardiac activity, into the continuous flow observed in peripheral circulation. Part of the energy produced by the left ventricular systole is used for the stretching of arteries and it is stored in their walls. During diastole, this energy recoils the aorta and squeeze out blood into microcirculation, ensuring a continuous flow to the tissues (64,65). In essential hypertension, remodeling occurs not only in small arteries but also in the macrocirculation (66,67). Large conduit arteries (such as aorta and its branches) develop arteriosclerosis of the media. This remodeling is characterized by an increase in intima-media thickness with a lumen enlargement of proximal elastic arteries and it is a compensation mechanism in order to normalize circumferential wall stress (65). Elastic fibers in the media become thinner and frail undergoing fragmentation with a parallel increase in collagen deposition and a consequent reduction in distensibility (62,66). Aging and BP are the two main determinant of arterial stiffness, which is influenced also by diabetes mellitus, obesity and metabolic syndrome. In the Framingham Heart Study, increased large artery stiffness, measured as pulse wave velocity, and aortic root enlargement were seen to be associated with a higher risk of cardiovascular disease (5,68). Pulse wave velocity correlates with hypertensive heart disease and microalbuminuria (69,70).

In fact, arterial stiffness has unfavorable consequences from a hemodynamic point of view. The increase in the speed of the incident and the reflected wave causes them to merge earlier, in the first part of the systole, increasing the systolic BP (with an increased afterload), reducing the diastolic BP (with a reduction in myocardial blood flow), and increasing the pulse pressure (66). In addition, with the elastic arteries becoming more rigid than the muscular ones, a reversion in the normal center-periphery stiffness gradient occurs, which is mainly responsible for the reflection of the sphygmoc wave (4,66). Hence, the reflection site moves more distally and the reflected wave is decreased, increasing

peripheral transmission of a large incident wave that exposes peripheral arteries and arterioles to harmful levels of pressure plasticity, contributing to alterations of microcirculation and, in the end, of nutrition and oxygenation of peripheral tissues (heart, brain, kidneys, limbs) as well as elimination of waste products (62,66).

It is still difficult to establish a temporal or a linear relationship between small and large artery alterations in essential hypertension. The most likely relationship is actually a cross-talk between micro- and microcirculation that may trigger a vicious circle (62,66). Hypertension causes the degeneration of large arteries and stiffness with consequent higher central systolic and pulse pressure, and microvascular alteration such as eutrophic remodeling, impaired vasodilatation, and microvascular rarefaction. Small arteries remodeling and rarefaction increase total peripheral resistance and amplifies mean BP (62,66). Indeed, in essential hypertension, MLR of small resistance arteries and pulse wave velocity are independent determinants of central systolic BP (71). Moreover, many indices of large artery stiffness (e. g. pulse pressure, pulse wave velocity) are associated with indices of microvascular damage (WLR and MLR respectively) (72,73).

Drugs that improve microvascular structure are particularly effective also in reducing central blood pressure, thus probably providing an additional benefit (4,62,69,74,75), most likely by slowing down the reflection of BP waves from the distal reflection sites, close to the microcirculation (4,62,66,69,74,75).

Pathophysiological consequences of the regression of small artery remodeling might be: a better blood pressure control, taking advantage of a reduced vascular reactivity (4,35); an improvement of the organ flow reserve, in particular in the heart (4,35,58); and an effective reduction of central blood pressure (4,62,66,69,74,75).

## CONCLUSIONS

In the hypertensive microcirculation wall thickness is increased in relation to internal lumen, and that this alteration contributes to the increase in peripheral resistance observed at the microvascular level (4). Microvascular structural alterations might also impair organ flow reserve (3,4,10,35,36), and this may play a role in the maintenance/progressive worsening of hypertensive disease. Therefore, an increased MLR in small resistance arteries may predict the development of hypertension-mediated organ damage/cardiovascular events, as well as complications of the disease (43,44).

There is a need for non-invasive techniques, in order to allow for a wider application of the evaluation of microvascular morphology, to better stratify cardiovascular risk and to better evaluate the effects of antihypertensive therapy (4,27). In this regard, techniques that allow an evaluation of retinal artery morphology seem to be a promising approach (27).

In conclusion, the evaluation of microvascular structure is progressively moving from bench to bedside (3,4,27), and could, in the near future, represent an evaluation to be performed in the majority, if not in all hypertensive patients (3,4,27). The most recent demonstration of a possible prognostic relevance of non-invasive measures of microvascular structure by Adaptive Optics represent a relevant contribution, although this evidence has to be confirmed by other studies; in addition, we do need a similar demonstration of a prognostic relevance of changes of indices of microvascular structure evaluated non-invasively observed during antihypertensive treatment.

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