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13.1 Plethysmography

The evaluation of minimum vascular resistance in the forearm with a plethysmographic technique is one of the earliest methods employed for the assessment of the microcirculation. Maximum postischemic flow is indeed correlated with the ratio between wall thickness and internal lumen in resistance arterioles [1]. For such an evaluation, it is therefore mandatory that the vascular district investigated is at a real maximum vasodilatation. In humans, this may be obtained by a combination of ischemia, muscular effort and, possibly, heat. It is not possible to obtain maximal flow with pharmacological approaches, such as the administration of acetylcholine, isoproterenol, adenosine, or sodium nitroprusside [2, 3]. From the maximum postischemic blood flow, it is possible to calculate minimum vascular resistance, which represents an indirect index of microvascular structural alterations, with the additional advantage of an in vivo evaluation [2, 3]. The plethysmographic technique requires the occlusion of the brachial artery of the dominant arm, through the inflation of a sphygmomanometric bladder up to 300 mmHg for 13 min and then a dynamic exercise (20–30 handgrips against the resistance offered by a rubber ball). The arterial occlusion is rapidly removed, while venous occlusion is maintained (around 60 mmHg of pressure in the sphygmomanometric bladder). Arterial flow is measured every 10 s for 3 min by a mercury strain gauge, which evaluates the increased volume of the forearm. In the absence of venous backward flow, the increased forearm volume is proportional to the arterial flow. The mean blood pressure, evaluated with an invasive or noninvasive method, divided by maximum arterial flow, allows the calculation of minimum vascular resistance.

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13.2 New Techniques of Evaluation of Microcirculation

Although the prognostic value of structural alterations in small subcutaneous arteries has been confirmed by two independent studies [4–6], according to the guidelines for the management of arterial hypertension of the European Society of Hypertension and of the European Society of Cardiology, “an increase in the wall-lumen ratio of small arteries can be measured in subcutaneous tissues obtained through gluteal biopsies. These measurements can demonstrate early alterations in diabetes and hypertension and have a predictive value for CV morbidity and mortality, but the invasiveness of the method makes this approach unsuitable for general use” [7].

Therefore, the development of new, noninvasive approaches for the evaluation of microvascular damage is needed. The interest of researchers was focused, in the last decade, on the retinal vascular district, since it represents the only microvascular bed that may be directly viewed with relatively simple approaches, such as an ophthalmoscope or a slit lamp [8]. Cerebral and retinal circulation share anatomic, physiological, and embryological features [9]. The same kind of structural alterations previously observed in subcutaneous small resistance arteries are also present in cerebral small arteries of hypertensive patients [10].

One of the first attempt to precisely quantify structural alterations of retinal microcirculation was made by Wong et al. [11]. By means of an automated computerized method, the authors have calculated the ratio between the arteriolar and venular external diameters (arteriolar to venular ratio (AVR)) in circular segments of the retina. Such a ratio resulted smaller in hypertensive patients compared with normotensive controls [11].

However, the prognostic significance of AVR is still controversial, since a correlation between AVR and incidence of cardiovascular events was detected only in women [11]. Furthermore, some studies have challenged the ability of the AVR to correctly stratify hypertensive patients according to the extent of target organ damage. Indeed, no relationship between quartiles of AVR and left ventricular mass, carotid artery intima-media thickness, or urinary albumin excretion was observed [12, 13].

An additional approach was proposed by Hughes et al. [14]. They demonstrated the possibility to quantify morphological changes in retinal vascular architecture by means of a dedicated software. In their study, essential hypertension was associated with an increase in the arteriolar length-to-diameter ratio [14]. There were also alterations in arteriolar morphology indicative of rarefaction, including a marked reduction in the number of terminal branches in essential hypertensive patients compared with normotensive subjects. These changes in the arteriolar network were exaggerated in patients with malignant hypertension [14]. The authors' conclusion was that “hypertension is associated with marked topological alterations in the retinal vasculature, and quantification of these changes may be a useful novel approach to the assessment of target organ damage in hypertension” [14]. The same authors have demonstrated that antihypertensive drugs might beneficially affect some of these parameters [15]. Presently, however, there are no data about relationships between these topological parameters and target organ damage or with structural

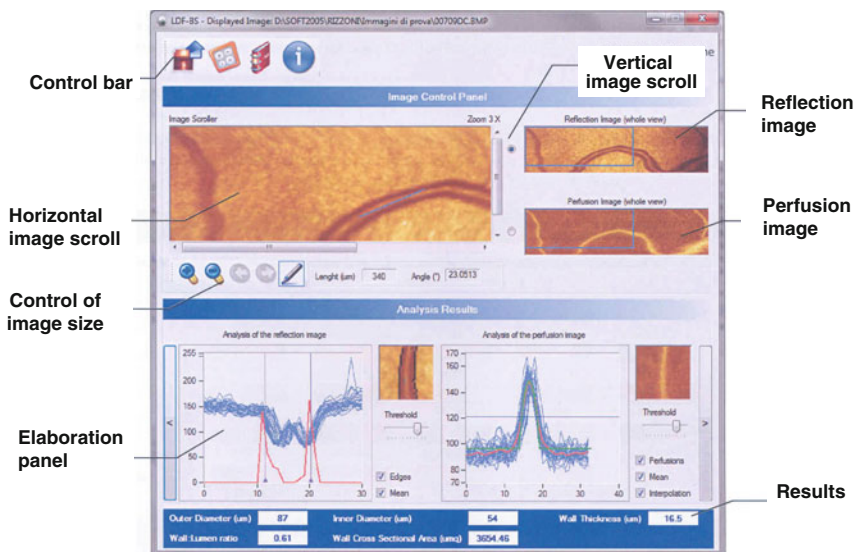


Fig. 13.1 Evaluation of small retinal artery morphology by scanning laser Doppler flowmetry and automatic full-field perfusion imaging analysis: example of the program output (Clinica Medica, University of Brescia; Reproduced from Rizzoni et al. [21], with permission)

alterations in other vascular beds; thus this approach, although stimulating and promising, needs further application and confirm.

More recently, Harazny et al. proposed a further, interesting and promising approach [16]. The method is based on the association between a confocal measurement of the external diameter of retinal arteriole and an evaluation of the internal diameter with a laser Doppler technique. The comparison between the two images, defined as “reflection image” and “perfusion image,” is made by a dedicated software [16] (Fig. 13.1). From these two measurements, it is relatively easy to calculate the ratio between wall thickness and internal lumen (WL) [16]. The same authors, using this approach, based on a scanning laser Doppler flowmetry (Heidelberg Retinal Flowmeter, Heidelberg Engineering, Germany), could observe that WL is increased in untreated essential hypertensive patients compared with normotensive controls [17] and that an even more marked increase is present in hypertensive patients with a history of cerebrovascular event [16]. WL of retinal arterioles was closely related with blood pressure values [16], included those recorded on treatment [17]. Finally, a close relationship was observed between WL and urinary albumin excretion, a marker of the microvascular damage at the kidney level [18]. When WL and AVR of retinal vessels were evaluated in the same patients, only the first parameter was progressively higher comparing normotensives, treated hypertensives, and hypertensives with a history of a cerebrovascular event, and these differences closely paralleled those observed for carotid artery intima-media thickness [19]. Intraobserver and interobserver variation coefficients were quite satisfactory, being below 10 % [20].

A recent study compared in the same subjects WL of retinal arterioles evaluated with scanning laser Doppler flowmetry and media/lumen ratio of subcutaneous small resistance arteries evaluated by wire micromyography, which is commonly considered the reference approach for the measurement of structural alterations in the small vessels. A rather good agreement between the two techniques, with a Pearson's correlation index above 0.76, was observed [21].

Recent evidence, obtained by both micromyographic approaches [22], as well as by the evaluation of retinal arteriolar morphology by scanning laser Doppler flowmetry [23, 24], suggests that presence of structural alterations of small resistance arteries may be associated with the increase in large arteries stiffness and possibly contribute to an increase in central pressure by increasing the magnitude of wave reflections.

Conclusions

In experimental hypertension, the increase in peripheral resistance occurs at the microvascular level. It was clearly demonstrated that wall thickness is increased in relation to internal lumen and that this alteration contributes to peripheral resistance. The increased media/lumen ratio may impair organ flow reserve [25]. This may be important in the maintenance and, probably, also in the progressive worsening of hypertensive disease. The evaluation of microvascular structure is not an easy task. The techniques with highest accuracy, such as wire or pressure micromyography, have the limitation of requiring biological samples, obtained by surgical approaches (e.g., gluteal biopsies). However, the presence of structural alterations evaluated by such approaches represents a prognostically relevant factor, in terms of development of target organ damage or cardiovascular events, thus allowing the prediction of hypertension complications [26, 27].

New, noninvasive techniques are needed before suggesting extensive application of the evaluation of microvascular morphology for the cardiovascular risk stratification in hypertensive patients. Some new techniques for evaluation of microvascular morphology in the retina, presently under clinical investigation, seem to represent a promising and interesting future perspective.

Presently, we may safely state that the evaluation of microvascular structure is progressively moving from bench to bedside [28], and it could represent, in the immediate future, an evaluation to be performed in all hypertensive patients, in order to obtain a better stratification of cardiovascular risk, and perhaps, it might be considered as an intermediate end point in the evaluation of the effects of antihypertensive therapy [29, 30].

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