Relationship of Wall-to-Lumen Ratio of Retinal Arterioles With Clinic and 24-Hour Blood Pressure

Massimo Salvetti, Claudia Agabiti Rosei, Anna Paini, Carlo Aggiusti, Anna Cancarini, Sarah Duse, Francesco Semeraro, Damiano Rizzoni, Enrico Agabiti Rosei, Maria Lorenza Muiesan

Abstract—Wall-to-lumen ratio of retinal arterioles might serve as an in vivo parameter of vascular damage. We analyzed the impact of brachial clinic blood pressure (BP), of central BP, and of 24-hour BP on wall-to-lumen ratio (WLR) of retinal arterioles. In 295 subjects (147 men; age range, 22–72 years; mean age, 54±7 years), WLR of retinal arterioles was assessed in vivo using scanning laser Doppler flowmetry. In addition, clinic and 24-hour BP values were measured. Central hemodynamics was assessed by pulse wave analysis. In treated patients with essential hypertension (n=100), a higher WLR (0.29±0.18 versus 0.23±0.13; P=0.009) was observed in comparison with normotensive individuals (n=119); no significant differences were observed between treated and untreated hypertensive patients (0.29±0.18 versus 0.28±0.18; P=0.7). WLR of retinal arterioles was significantly related to clinic systolic (r=0.18; P=0.002) and pulse pressure (r=0.20; P=0.001), to 24-hour systolic (r=0.25; P=0.0001) and pulse pressure (r=0.17; P=0.005), and to central systolic (r=0.16; P=0.006) and pulse pressure (r=0.18; P=0.002). Multiple regression analysis revealed that only mean systolic 24-hour BP was independently associated with an increased WLR of retinal arterioles. In this large group of hypertensive patients and normotensive individuals, 24-hour systolic BP seems to be the strongest determinant of increased WLR of retinal arterioles. (Hypertension. 2014;63:1110-1115.)

Key Words: blood pressure monitoring, ambulatory pulse wave analysis retinal vessels vascular stiffness

Systemic arterial hypertension is associated with vascular changes in the retina that may occur in acute stages or develop chronically.1 Retinal microcirculation represents, perhaps, the only microvascular district that may be directly observed and evaluated by a relatively simple funduscopic examination. Clinical fundoscopic assessment of retinal microcirculation is still based on a classic approach used to detect structural alterations of retinal arterioles associated with chronic blood pressure (BP) elevations, as well as long-lasting abnormalities in insulin sensitivity and blood glucose profile. However, several studies have proved a weak clinical usefulness of Keith–Wegener classification, because of poor reproducibility and association with other indices of target organ damage.2,3 Funduscopic examination has gained new popularity, thanks to the availability of standardized procedures based on computer-assisted evaluation of digitized retinal photographs.4–6 The arteriovenous ratio of retinal arterioles and venules, proposed with these techniques, was shown to predict the incidence of stroke and cardiovascular morbidity, although the methodology with digitized photographs and the need of a core reading center prohibited its widespread clinical use.7 Wall-to-lumen ratio (WLR) of retinal arterioles, measured using scanning laser Doppler flowmetry (SLDF), has been proposed as an in vivo parameter of vascular damage for large-scale evaluation.8–10 This index seems to be a robust indicator of the severity of hypertension9 and of the presence of early renal damage.10 WLR of the retinal arterioles was found to be increased in patients with cerebrovascular events2 and related to the extent of intima-media thickness in the carotid artery.11 In addition, it was demonstrated that WLR of retinal arterioles assessed with SLDF provides information similar to that obtained with the micromyographic measurement of media-to-lumen ratio of subcutaneous small arteries, generally considered the gold standard approach to the evaluation of microvascular structure.12

Central BP, indicative of changes in large conduit arteries, was found to be an independent determinant of vascular remodeling in retinal arterioles,13 supporting the concept that changes in macrovasculature and microvasculature are strongly interrelated and confirming previous results obtained with invasive assessment of small artery remodeling by micromyography.14

Because the possible interrelationship between alterations in retinal arterioles and 24-hour BP has not been extensively evaluated and because the influence of ambulatory BP monitoring in respect to peripheral and central hemodynamics on retinal structure deserves further investigation, we considered worthwhile assessing the relationship of WLR of retinal arterioles with clinic brachial and 24-hour ambulatory BP and with central BP in normotensive subjects and in patients with primary hypertension.

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1110
Methods
Between May 2010 and April 2013, all of the subjects participating in the Vobarno study and consecutive patients with primary hypertension attending the outpatient clinic of our institution (Medical School, University of Brescia) were asked to participate in this study. Inclusion criteria included absence of secondary causes of hypertension and of previous cardiovascular diseases, whereas exclusion criteria were previous cardiovascular and life-threatening disease, any condition preventing technical quality of ambulatory BP monitoring such as atrial fibrillation, and other major dysrhythmias.

The protocol of the study was approved by the ethics committee of our institution, and the study was conducted in accordance with the Declaration of Helsinki and the principles of good clinical practice. Informed consent was obtained from each participant. The procedures followed were in accordance with institutional guidelines.

All of the patients underwent the following procedures: (1) office BP measurement, (2) 24-hour ambulatory BP monitoring, (3) blood and urine sampling, (4) pulse wave velocity (PWV) evaluation, and (5) retinal measurement of WLR.

Venasous blood samples were taken with participants in supine position for standard hematology and serum biochemistry tests. The abbreviated Modification of Diet in Renal Disease Study equation was used to estimate glomerular filtration rate (eGFR; in ml/min per 1.73 m²) according to the following formula: 186.3×(serum creatinine in mg/dl−1.154)×(age in years−0.203)×1.212 (if black)×0.742 (if female patient). Of 322 participants (all white Europeans) included in the present study, measurements could not be performed because of retraction problems in 27 subjects, and therefore, data of 295 subjects were reported. One hundred seventy-six patients had a diagnosis of primary hypertension, whereas 119 were normotensive subjects. Among hypertensive patients, 76 were never treated, and 100 had been previously treated for various periods of time with dihydropyridinic calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blocker, and diuretics.

Thirty-five patients with hypertension had also a diagnosis of type 2 diabetes mellitus. The presence of type 2 diabetes mellitus was established according to the Guidelines of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Clinic BP was measured using an Omron 705 C oscillometric device. Three measurements were performed and the average was retained.

Ambulatory BP was recorded using a validated oscillometric device (SpaceLabs model 90207; SpaceLabs Inc, Redmond, WA) set to take readings every 20 minutes during daytime (defined as 07:00 to 22:59 hours) and 30 minutes during nighttime (defined as 23:00 to 06:59 hours), with a total number of 64 measurements per day. Subjects were fitted with the recorder at 09:00 hours and removed at 10:00 hours the following day (25 hours of monitoring). Subjects were allowed to follow their daily normal routines after they left the laboratory and were requested to refrain from heavy physical exercise and to keep a diary indicating location and activities of the day. No recordings were requested to refrain from heavy physical exercise and to keep a 24-hour diary indicating location and activities of the day. No recordings were requested to refrain from heavy physical exercise and to keep a 24-hour diary indicating location and activities of the day.

PWV was measured at carotid and femoral locations using the foot-to-foot velocity method. Waveforms were obtained transcutaneously over the common carotid artery and the right femoral artery, and time delay (transit time, t) was measured between the feet of 2 waveforms (Complior). The distance (D) covered by the waves was assimilated to the distance measured between 2 recording sites (carotidfemoral distance). PWV was calculated as: \( \text{PWV} = \frac{\text{D}}{t} \); all calculations, including the measurement of parameters >5 to 10 cardiac cycles, were automated. As recently suggested, we calculated PWV by the formula \( (D/t) \times 0.80 \); accordingly, an increase of PWV >10 m/s, was considered a macrovascular target organ damage.

Applanation tonometry was also performed using a Sphymgo-Cor device (Atcor), as described and recommended previously. Briefly, applanation probe was positioned on the radial artery (right arm), and optimal applanation was obtained using visual inspection and following built-in quality control indices. BP was measured using an Omron 705 C oscillometric device, and radial waveforms were calibrated using brachial systolic BP and diastolic BP. The central aortic waveform was calculated by the device software using generalized transfer function. BP values were derived from this with the technique of pulse wave analysis. The merging point of the incident and the reflected wave (inflection point) were identified on the generated aortic pressure waveform. Augmentation pressure was the maximum systolic pressure minus pressure at the inflection point. Augmentation index was defined as augmentation pressure divided by pulse pressure and expressed as a percentage.

All patients underwent an evaluation of retinal arteriolar morphol- ogy. WLR of retinal arterioles was assessed using SDLF at 670 nm (Heidelberg Retina Flowmeter; Heidelberg Engineering, Heidelberg, Germany), an established method to investigate retinal perfusion.

Briefly, arteriole of size between 80 and 140 mm of the superfi- cial retinal layer in a retinal sample of 2.56×0.64×0.30 mm was scanned <2 seconds, at a resolution of 256 points×64 lines×128 lines. Measurements were performed in the juxtapapillary area of the right eye, 2 to 3 mm on the temporal superior side of the optic nerve; the mean from 3 measurements was taken. Only arterioles that could be unambiguously discriminated and clearly identified on the temporal superior side of the optic nerve were selected. Images of arterioles without sharp contrast to the retina or with crossing and overlapping of venules, curved arterioles, or arterioles with >1 bifurcation on the image and images with >4 eye movements were excluded. Examination was performed without mydriasis, in sitting position after 20 minutes of rest, at room temperature, and daylight conditions between 08:00 and 12:00 hours, but before lunch. Analyses of diameters were performed offline with automatic full-field perfusion imaging analysis program (Nirox Optoelectronics, Brescia, Italy). Outer arteriole diameter was measured in reflection images, and lumen diameter was measured in perfusion images; WLR was calculated using the formula \( (\text{arteriole diameter}−\text{lumen diameter})/\text{lumen diameter} \). The coefficients of variation (10 patients, 2 observers or 10 patients, 2 readings of the same observer 1 day apart) were 13% and 11%, respectively. Interclass correlation coefficients were 0.933 (intragrader reproducibility) and 0.927 (intergrader reproducibility), indicating excellent reproducibility, as also confirmed by Bland–Altman analysis with Pitman test of difference in variance (differences between observations were those expected on a casual basis; \( P<0.80 \)).

Statistical Analysis
All data are expressed as mean±SD, unless otherwise stated. Differences between groups were evaluated by Student unpaired t test or ANOVA. Distribution of categorical variables between groups was evaluated by χ² test. Relationships between variables were assessed by the calculation of Pearson correlation. All parameters were normally distributed. A stepwise multivariate regression analysis was then performed. The following independent variables were considered: age; sex; smoking status; body mass index; systolic, diastolic and pulse pressure; heart rate; serum glucose; total cholesterol; and eGFR. The dependent variable was WLR of retinal arterioles.

All statistical tests were 2-tailed. A value of \( P<0.05 \) was considered statistically significant. All analyses were performed with SPSS software (version 18.0; SPSS Inc, Chicago, IL).

Results
Demographic characteristics of normotensive individuals and hypertensive patients enrolled in the study are detailed in Table 1. Normotensive subjects were more frequently women and had a lower body mass index compared with hypertensive
patients, both treated and untreated. Treated hypertensive patients were slightly older than untreated hypertensive patients.

All BP values were higher in untreated hypertensive patients as compared with normotensive individuals, whereas systolic and diastolic pressure was higher in treated hypertensive patients as compared with normotensive individuals.

Heart rate was higher in untreated hypertensive individuals as compared with normotensive individuals (Table 1). Glycemia was higher and HDL cholesterol was lower in hypertensive patients; low-density lipoprotein-cholesterol was lower in treated than in untreated hypertensive patients.

Wall thickness and WLR of retinal arterioles progressively increased from normotensive individuals to untreated and treated hypertensive patients (P for a trend=0.001) and were significantly greater in hypertensive patients, compared with normotensive individuals (P<0.05 for both), whereas no differences were observed among the 3 groups for inner and outer diameters of retinal arterioles (see Figure).

At univariate correlation analyses, no correlation was observed between WLR and age (r=0.007; P=0.91), body mass index (r=0.074; P=0.1), fasting glucose (r=0.048; P=0.43), low-density lipoprotein-cholesterol (r=−0.014; P=0.83), serum creatinine (r=0.076; P=0.21), and eGFR (r=−0.064; P=0.31), respectively.

BP values, measured during 24-hour ambulatory monitoring, were higher in hypertensive patients, both untreated and treated, as compared with normotensive individuals (Table 2).

WLR of retinal arterioles was significantly related to clinic systolic BP (r=0.18; P=0.002) and pulse pressure (r=0.20; P=0.001), to 24-hour systolic BP (r=0.25; P=0.0001) and pulse pressure (r=0.17; P=0.005), and to central systolic BP (r=0.16, P=0.006) and central pulse pressure (r=0.18; P=0.002; Table 2). When daytime and nighttime mean BPs were analyzed separately, WLR was significantly related to daytime systolic (r=0.27; P=0.0001) and diastolic BP (r=0.20; P=0.001) and to nighttime systolic (r=0.17; P=0.005) and diastolic BP (r=0.15; P=0.01). No significant correlation was found between WLR and augmentation index or augmentation pressure, whereas a significant correlation was observed between WLR and PWV (r=0.17; P=0.005; see Figure).

We applied a multivariate regression analysis using WLR of retinal arterioles as dependent variable and including all common cardiovascular risk factors (age, sex, smoking status, body mass index, serum glucose, serum low-density lipoprotein-cholesterol, and eGFR) 24-hour, and central BP values. Mean systolic BP measured during 24 hours, but not central systolic BP, proved to be the strongest predictor independently related to WLR of retinal arterioles (Table 3).

By including PWV in an alternative model (Table 3, model 2), the parameters that remained independently related to WLR of retinal arterioles were PWV and 24-hour mean BP. Finally, if we considered PWV and central systolic BP (instead of 24-hour BP), only PWV, but not central BP, was an independent predictor of WLR (Table 3, model 3).

Discussion

In the present study, for the first time to our knowledge, we report a correlation between indices of retinal arterioles structure and 24-hour systolic and pulse pressure. In addition, we were able to confirm that changes in microvasculature, indicated by retinal arterioles WLR, are related to aortic stiffness, independently of other classical cardiovascular risk factors.

It is well known that hypertensive retinopathy is related to both the presence and severity of hypertension, although the association between specific signs of hypertensive retinopathy and BP may be different according to age and other cardiovascular risk factors. In elderly people, for example, the association between BP and retinal microvascular signs becomes weaker and possibly reflects greater sclerosis of retinal arterioles. Studies using semiautomated computerized analysis of retinal vessels have demonstrated that retinal arteriolar narrowing strongly correlates with higher clinic BP, and patients

Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normotensives (n=119)</th>
<th>HT Untreated (n=76)</th>
<th>HT Treated (n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>46/74</td>
<td>42/33</td>
<td>59/41*</td>
<td>0.01</td>
</tr>
<tr>
<td>Age, y</td>
<td>55±4</td>
<td>53±8</td>
<td>55±7†</td>
<td>0.05</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>126±15</td>
<td>146±19*</td>
<td>136±17*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>74±8</td>
<td>89±10*</td>
<td>82±9*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean BP, mmHg</td>
<td>90±9</td>
<td>106±11*</td>
<td>97±9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate, beats per min</td>
<td>62±9</td>
<td>69±11*</td>
<td>66±12</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25±4</td>
<td>27±5*</td>
<td>28±5*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
<td>4.94±1.0</td>
<td>5.44±1.17*</td>
<td>5.3±1.0*</td>
<td>0.003</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.56±0.9</td>
<td>5.8±0.9</td>
<td>5.48±1.01</td>
<td>0.06</td>
</tr>
<tr>
<td>Tryglicerides, mmol/L</td>
<td>1.24±0.54</td>
<td>1.64±0.93</td>
<td>1.8±1.59*</td>
<td>0.01</td>
</tr>
<tr>
<td>LDL-cholesterol,mmol/L</td>
<td>3.39±0.8</td>
<td>3.72±0.85*</td>
<td>3.33±0.82†</td>
<td>0.02</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>96±18</td>
<td>94±15</td>
<td>94±18</td>
<td>0.45</td>
</tr>
<tr>
<td>Smoking, yes/no, n</td>
<td>59/60</td>
<td>36/40</td>
<td>55/45</td>
<td>NS</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HT, hypertensives; LDL, low-density lipoprotein; and NS, nonsignificant.

*P<0.05 at least vs normotensives.
†P=0.05 at least vs HT untreated.
with more elevated BP values also had increased number of hypertensive retinal vascular signs.25,26

Few studies have analyzed retinal structure changes as related to 24-hour BP, with conflicting results. Hypertensive retinopathy, defined according to the Keith–Wegener classification, was found to be more prevalent in patients with higher 24-hour systolic loads,27 whereas Cuspidi et al did not find any difference in clinic and 24-hour BP when comparing patients with grade I or II hypertensive retinopathy.3 The new method of assessment of structural abnormalities in the retinal vasculature, proposed by Schmieder and Michelson, may give a quantitative measure of WLR of retinal arterioles using SDLF.24 Using this approach, it was demonstrated that WLR of retinal arterioles increased in untreated hypertensive patients9 as well as in treated patients with cerebrovascular events,7 representing a robust indicator of the severity of hypertension. In addition, WLR of retinal arterioles seems to correlate with indices of microvascular damage in other vascular districts, such as albumin excretion by the kidney10 and with carotid artery intima-media thickness.11 More recently, the measurement of retinal morphology by SDLF was validated against the present gold standard for measurement of microvascular structure, that is, wire or pressure micromyography applied to subcutaneous small arteries obtained through gluteal biopsies.12

The results of the present study confirm previous findings about the role of BP increase measured during 24 hours on remodeling of subcutaneous small resistance arteries, examined in vitro28–30; we found a correlation between small artery structure and both clinic and 24-hour systolic and diastolic BP, and the correlation was more strict after exclusion of patients with renovascular hypertension29 to rule out the possible influence of other factors, such as circulating neurohormonal factors, on remodeling in subcutaneous resistance arteries.31,32

In addition to BP, several neurohormonal factors have been suggested to impact arterial remodeling, including dietary salt, angiotensin II, endothelin-1, and insulin; this might explain why the correlation between 24-hour BP and retinal arteriolar structure was not very strict, albeit statistically significant. We did not assess these parameters, and therefore this study cannot give any conclusions with respect to their role on retinal arteriolar structure.33

We have confirmed that changes in microvasculature, as indicated by WLR of retinal arterioles, are related to PWV, the goal standard for aortic stiffness evaluation. These data further support the concept that changes in macrovasculature and microvasculature are strongly interrelated, as suggested by our previous investigation obtained with invasive assessment.

### Table 2. BP Values During Ambulatory Monitoring

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normotensives (n=119)</th>
<th>HT Untreated (n=76)</th>
<th>HT Treated (n=100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h systolic BP, mmHg</td>
<td>120±11</td>
<td>133±10*</td>
<td>126±13†</td>
<td>0.001</td>
</tr>
<tr>
<td>24-h diastolic BP, mmHg</td>
<td>75±7</td>
<td>85±8*</td>
<td>79±9†</td>
<td>0.001</td>
</tr>
<tr>
<td>24-h pulse pressure, mmHg</td>
<td>45±7</td>
<td>48±8*</td>
<td>47±8</td>
<td>0.003</td>
</tr>
<tr>
<td>24-h heart rate, beats per min</td>
<td>72±8</td>
<td>74±8</td>
<td>73±9</td>
<td>0.30</td>
</tr>
<tr>
<td>Daytime systolic BP, mmHg</td>
<td>123±10</td>
<td>137±10*</td>
<td>130±13†</td>
<td>0.001</td>
</tr>
<tr>
<td>Daytime diastolic BP, mmHg</td>
<td>79±8</td>
<td>89±8*</td>
<td>83±9†</td>
<td>0.001</td>
</tr>
<tr>
<td>Nighttime systolic BP, mmHg</td>
<td>116±11</td>
<td>126±11*</td>
<td>121±14†</td>
<td>0.001</td>
</tr>
<tr>
<td>Nighttime diastolic BP, mmHg</td>
<td>70±8</td>
<td>78±8*</td>
<td>75±10†</td>
<td>0.001</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; and HT, hypertensives.

*P<0.05 at least vs normotensives.

†P<0.05 at least vs HT untreated.
Aortic stiffening facilitates the transmission of pulsatile energy into the microcirculation of brain and kidneys, leading to microvascular damage and explaining the known association between aortic stiffness and end-organ damage. Alternatively, abnormalities in small artery structure could increase mean arterial pressure. A possible future perspective related to our results is represented by the wide use of a noninvasive approach for stratification of risk in the majority of hypertensive patients, because microvascular structure may represent an intermediate end point in the evaluation of the effects of antihypertensive treatment.

In conclusion, an evaluation of arterioles in fundus oculi by micromyography allows one to assess the relationship between circadian variability of pulse pressure amplification and microvascular retinal changes. Multiple regression analysis was performed in a relatively small population, whereas ≈10 variables were included in the model. Therefore, results obtained with this statistical approach should be considered with caution.

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### Disclosures

None.

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Novelty and Significance

**What Is New?**
- The study describes the correlation between wall-to-lumen ratio (WLR) of retinal arterioles measured by laser Doppler flow technique and either brachial blood pressure, measured in the clinic and by 24-hour ambulatory monitoring or central blood pressure.

**What Is Relevant?**
- The results show a correlation between indices of retinal arterioles structure and 24-hour systolic and pulse pressure, independent of traditional risk factors and of aortic stiffness.
- Changes in microvasculature, such as indicated by WLR of retinal arterioles, are related to pulse wave velocity, the gold standard for aortic stiffness evaluation, further supporting the concept that changes in macrovasculature and microvasculature are strongly interrelated.

**Summary**
In a cohort of hypertensive patients and normotensive individuals, 24-hour systolic BP seems to be the strongest determinant of increased WLR of retinal arterioles, more closely related to retinal microvasculature changes than a single measurement of aortic central pressure.
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