Pulsatile Hemodynamics and Microcirculation
Evidence for a Close Relationship in Hypertensive Patients

Maria Lorenza Muiesan*, Massimo Salvetti*, Damiano Rizzoni, Anna Paini, Claudia Agabiti-Rosei, Carlo Aggiusti, Fabio Bertacchini, Deborah Stassaldi, Alice Gavazzi, Enzo Porteri, Carolina De Ciucesi, Enrico Agabiti-Rosei

Abstract—The possible relationships between indicators of small resistance artery structure and of arterial stiffness and central hemodynamics have not yet been evaluated. Aim of this study was to assess the relationship between indicators of large arteries stiffness, including carotido-femoral pulse wave velocity and of vascular alterations in small resistance arteries (media/lumen ratio, M/L) in patients with primary and secondary hypertension. In 73 patients (mean age, 53±14 years, 34 females, 25 with type 2 diabetes mellitus, 18 never treated) with essential (n=37) and secondary (n=36) hypertension, carotido-femoral pulse wave velocity was measured. In all patients, small resistance arteries were dissected from subcutaneous fat biopsies and mounted on an isometric myograph, for the measurement of the M/L. Pulse wave analysis was performed in 67 patients. M/L ratio was significantly related to brachial systolic blood pressure and pulse pressure ($r=0.36$ and $0.31$, $P<0.001$, respectively) and to central systolic and pulse pressure ($r=0.44$ and $0.42$, $P<0.001$, respectively). A positive correlation was observed between M/L ratio and carotido-femoral pulse wave velocity ($r=0.45$; $P<0.001$); this correlation remained statistically significant after adjustment for age and mean blood pressure. M/L ratio was also associated to aortic augmentation index ($r=0.33$; $P=0.008$), and this correlations remained statistically significant after adjustment for potential confounders. In hypertensive patients, the 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. (Hypertension. 2013;61:130-136.)

Key Words: arterial stiffness microcirculation arterial hypertension small resistance arteries central blood pressure pulse wave velocity augmentation index

Arterial stiffness and small artery structural alterations play a key role in the pathophysiology of the cardiovascular system. Because of the viscoelastic properties of large arteries, the pulsatile pressure and flow that result from intermittent ventricular ejection are smoothed out, so that microvasculature mediates steadily the delivery of nutrients and oxygen to tissues. Large arteries become stiffer because of age-related processes, and under the influence of conditions such as hypertension, dyslipidemia, and diabetes mellitus. When the stiffness increases, the pulse wave is transmitted more rapidly and, once reflected from the peripheral vasculature (branching, resistance sites, and stenosis), returns to the heart during left ventricular contraction, resulting in a greater augmentation of the central aortic systolic pressure.1,2

In small resistance arteries, the remodeling process (thickened arterial wall together with a reduced lumen) represents an adaptive response to an increase in hemodynamic load and to humoral growth factors, playing an important role in the impairment of vasodilator reserve.3,4

Microvascular structure is not only the site of vascular resistance but also, probably, the origin of most of the wave reflections generating increased central systolic blood pressure (SBP) in the elderly,5 although the proper location of a reflection site is elusive.6 Several studies have demonstrated that aortic stiffness, measured by pulse wave velocity (PWV), may yield prognostic value for cardiovascular events beyond and above all cardiovascular risk factors.7,8 Structural alterations in the microcirculation (as indicated by greater values of media/lumen ratio [M/L] in subcutaneous small resistance arteries) have been also shown to predict the occurrence of cardiovascular events.5–11 Interestingly, in a high-risk population of hypertensive patients12 microvascular structure and pulse pressure, a rough index of large artery stiffness, were the only 2 predictors of cardiovascular events, thus suggesting that in high-risk individuals structural changes in the microcirculation and alterations on mechanical properties of large arteries are the 2 most important factors in predicting cardiovascular outcome.
Previous results evaluating the interrelations between indicators of small resistance artery structure and of large artery stiffness have shown that the stroke volume/pulse pressure ratio, an indirect index of large arteries compliance derived from echocardiographic left ventricular measurements, was significantly related to alterations in small resistance arteries (as measured by the M/L ratio). Large artery stiffening was demonstrated to be related to cerebral lacunar infarctions, which are usually expression of cerebral microvascular disease, to coronary microcirculation, and to the impairment of renal function.

Several hypotheses have been proposed to explain the relationship between large and small vessels disease. Cardiovascular risk factors may influence the development of vascular damage in both large and small arteries. Another possibility is that a decrease in aortic stiffness increases pulse pressure, and the exposure of small vessels to highly pulsatile pressure and flow could induce damage to the microcirculation. Finally, alterations in microvascular structure, such as increase in wall/lumen ratio and rarefaction, increase mean blood pressure (BP) exerting a load on nonmuscular components of the aortic wall increasing aortic stiffness. These hypotheses do not exclude each other and a bidirectional link could be speculated, leading to a vicious circle. Because the possible relationships between indicators of small resistance artery structure and of large artery stiffness have not yet been extensively evaluated, we considered worthwhile assessing the relationship among PWV, central BP, and vascular alterations in small resistance arteries (as measured by the M/L ratio) in patients with primary and secondary hypertension.

Methods

Seventy-three participants were included in the present study. Thirty-seven patients had a diagnosis of primary hypertension, whereas 36 had secondary forms of hypertension (19 primary aldosteronism, 5 Cushing disease, and 12 pheochromocytoma). Twenty-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. The diagnosis of secondary forms of hypertension was made on the basis of an indication for adrenal tumor resection, after proper investigation by imaging techniques and hormonal assessments.

Eighteen patients were never treated, and 55 individuals had been previously treated for various periods of time with dihydropyridinic calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics, but not β-blockers. Venous blood samples were taken with the participants in the supine position, for β-blockers. Venous blood samples were taken with the participants in the supine position, for determination of glomerular filtration rate (in mL/min per 1.73 m²) according to the following formula: 186.3 × (serum creatinine in mg/dL) × (age in years) × 1.212 (if black) × 0.742 (if female patient).

The protocol of the study was approved by the ethics committee of our institution (Medical School, University of Brescia), and informed consent was obtained from each participant. The procedures followed were in accordance with institutional guidelines.

BP was measured using an Omron 705 C oscillometric device. Three measurements were performed, and the average of 3 measures was retained.

PWV was measured at the carotid and femoral locations using the foot-to-foot velocity method. Waveforms are obtained transcutaneously over the common carotid artery and the right femoral artery, and the time delay (transit time [t]) is measured between the feet of the 2 waveforms (Compilior). The distance (D) covered by the waves has been assimilated to the distance measured between the 2 recording sites (carotido-femoral distance). PWV was calculated as: \[ PWV = \frac{D(m)}{t(s)} \] all calculations, including measurement of parameters over 5 to 10 cardiac cycles, were automated. As recently suggested, we used 80% of this distance as pulse wave traveled distance (d) and calculated PWV by the formula \( (D[m]/t[s]) \times 0.80 \); accordingly an increase of PWV, ≥10 m/s, was considered as macrovascular target organ damage.

In 67 of 73 patients, applanation tonometry was also performed using a Sphygmo-Cor device (Atcor), as described previously and recommended. Briefly, the 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 again using an Omron 705 C oscillometric device and radial waveforms were calibrated using brachial SBP and diastolic BP measured before and after applanation (average). The central aortic waveform was calculated by the device software using the generalized transfer function. BP values were derived from the curve. Augmentation index (Alx) and augmentation pressure were derived from this with the technique of pulse wave analysis. The merging point of the incident and the reflected wave (the inflection point) was identified on the generated aortic pressure waveform. Augmentation pressure was the maximum systolic pressure minus pressure at the inflection point. Alx was defined as the augmentation pressure divided by pulse pressure and expressed as a percentage.

Micromyography

All participants were submitted to a biopsy of subcutaneous fat from the gluteal or the anterior abdominal region. Subcutaneous small resistance arteries (100–300 μm of average diameter in relaxed conditions, 2 mm long) were dissected from the subcutaneous fat of the biopsies and mounted as a ring preparation on an isometric myograph, by threading onto 2 stainless steel wires, according to Mulvany–Halpern technique. The vessel internal circumference was set to give a wall tension of 0.1 mN/mm. Vessel wall thickness and media thickness were measured at 12 sites that were then averaged, using a light microscope with immersion lens (Lab 20; Carl Zeiss S.P.A., Milan, Italy) at x600 magnification, which provides a resolution of 0.2 mm. Lower magnification was used for measurement of the distance between the wires and length of the blood vessel. The resting tension–internal circumference relation was determined, and vessels were set to the normalized circumference L1, where L1 is equal to 0.9 L100 and L100 is equal to the internal circumference the vessels would have had in vivo, when relaxed and under a transmural pressure of 100 mm Hg, as described previously by Mulvany et al.

From 1L, the normalized internal diameter L1 was calculated. Assuming that the cross-sectional area remains constant when the vessel is extended to L1, the wall thickness and media thickness were automatically calculated also in normalized condition. Wall thickness and media thickness of blood vessels in normalized condition (vessels extended to L1) were obtained assuming a constant wall and media volume, from wall and media cross-sectional area calculated from wall and media thickness measured in unstretched vessels, as previously described.

From media thickness and normalized internal diameter, M/L ratio was calculated. Results from 2 different blood vessels in each participant were averaged to provide 1 mean observation per participant. Further details about the micromyographic technique of evaluation of small artery morphology are reported elsewhere. An M/L ratio ≥0.098 (ie, mean and median M/L ratio value observed in a large population previously examined) was considered as microvascular target organ damage.
Statistical Analysis

All data are expressed as mean±SD, unless otherwise stated. Relationships between variables were assessed by calculation of Pearson correlation. The diagnoses of secondary hypertension (yes/no) and of type 2 diabetes mellitus (yes/no) were considered as dummy variables. A stepwise multivariate linear regression analysis was performed to assess the independent correlation among M/L ratio, carotido-femoral PWV, and pulse wave analysis parameters, after adjustment for potential confounders, including age, body height, type 2 diabetes mellitus, body mass index, office BP, and office heart rate; the analysis, therefore, included all variables with significant relationships in univariate analyses with M/L ratio and carotido-femoral PWV, respectively. All the statistical tests were 2 tailed. A value of \( P<0.05 \) was considered statistically significant. All analyses were carried out with SPSS software (version 18.0; SPSS Inc, Chicago, IL).

Results

Demographic data of study population are shown in Table 1. In 25 patients PWV was >10 m/s, in 25 patients an increase in M/L was observed, and in 13 patients an increase of both PWV and M/L was found.

A significant correlation was observed between PWV and age, glycemia, estimated glomerular filtration rate, brachial SBP, pulse BP, and mean BP (Table 2). PWV was also related to the presence of diabetes mellitus but not of secondary hypertension.

A significant correlation was also observed between M/L ratio and age; M/L ratio was also significantly related to brachial SBP and pulse pressure (Table 2). No significant correlation was observed between M/L ratio and the diagnosis of diabetes mellitus or of secondary hypertension.

A positive correlation was observed between M/L and PWV (\( r=0.45; \ P<0.001 \)). This correlation remained statistically significant after adjustment for age and mean BP (\( R^2=0.20; \ P=0.048 \); Figure). M/L ratio was also associated with central systolic, pulse, and mean BPs, with augmentation pressure, with AIx (Table 2), and with pulse pressure amplification (\( r=0.25; \ P=0.04 \)). The independent relation between PWV and M/L ratio was confirmed in a stepwise multivariate linear regression model. PWV was independently related to M/L ratio together with age and mean BP, whereas diabetes mellitus and body mass index did not enter into the model (Table 3).

Linear stepwise multiple regression analysis was performed to evaluate the independent influence of several variables on central SBP and on AIx. Central SBP was independently related to carotido-femoral PWV and to M/L ratio, but not to age (Table 4). A higher AIx was independently associated with a greater M/L ratio together with height, heart rate, and SBP, whereas age and carotido-femoral PWV did not enter into the equation (Table 5).

Discussion

For the first time in our study, it has been demonstrated that the M/L ratio of subcutaneous small resistance arteries, an index of structural alteration in the microcirculation, is associated with large artery stiffness. We have observed a significant relationship between M/L ratio and PWV, which is independent of age and BP values, thus suggesting that structural alterations in small and large vessels may be reciprocally interrelated.

Previous studies had shown that an increase in aortic or carotid stiffness is associated with the degree of albuminuria and with the reduction of kidney function, or with the presence of white matter lesions or cognitive function decline, possibly suggesting that an alteration at the level of renal and cerebral microcirculation was associated with the loss of aortic distensibility.

Furthermore, in subjects free of cardiovascular disease aortic stiffness, evaluated by chest magnetic resonance imaging, was significantly increased in parallel with retinal arteriolar narrowing, independently of age, BP, diabetes

Table 1. Demographic Characteristics of Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>N=73</th>
<th>Range</th>
<th>N=67</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53±14</td>
<td>24–80</td>
<td>54±13</td>
<td>26–80</td>
</tr>
<tr>
<td>Female/male (n)</td>
<td>34/39</td>
<td>28/39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers, %</td>
<td>21</td>
<td></td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Brachial SBP, mm Hg</td>
<td>137±19</td>
<td>90–191</td>
<td>137±19</td>
<td>90–191</td>
</tr>
<tr>
<td>Brachial DBP, mm Hg</td>
<td>80±11</td>
<td>54–107</td>
<td>81±11</td>
<td>56–107</td>
</tr>
<tr>
<td>Brachial MBP, mm Hg</td>
<td>99±12</td>
<td>70–127</td>
<td>100±12</td>
<td>70–127</td>
</tr>
<tr>
<td>Brachial PP, mm Hg</td>
<td>56±16</td>
<td>30–112</td>
<td>56±16</td>
<td>30–112</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>66±13</td>
<td>40–100</td>
<td>66±12</td>
<td>40–91</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.9±8</td>
<td>19–57</td>
<td>29±7.5</td>
<td>19–54</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.99±0.98</td>
<td>2.66–7.24</td>
<td>4.9±0.98</td>
<td>2.66–7.24</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>94±27</td>
<td>18.5–174.7</td>
<td>84±24</td>
<td>22–146</td>
</tr>
<tr>
<td>Pulse wave velocity, m/s</td>
<td>9.25±2.1</td>
<td>4.96–15.56</td>
<td>9.25±2.1</td>
<td>4.96–15.56</td>
</tr>
<tr>
<td>Media/lumen ratio</td>
<td>0.09±0.02</td>
<td>0.06–0.18</td>
<td>0.09±0.02</td>
<td>0.06–0.18</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate.
mellitus, measures of atherosclerosis, and other vascular risk factors. The Atherosclerosis Risk in Communities (ARIC) Study showed an association between increased carotid artery stiffness determined from ultrasound examinations and smaller arteriolar/venule ratio, suggested to reflect retinal arteriolar narrowing.

Our data confirm previous findings, in which the presence of structural alterations of small vessels was measured indirectly or suspected on the basis of renal function derangement. In our study, we were able to directly investigate changes in small resistance arteries obtained from subcutaneous fat tissue of patients by using the micromyographic method, measuring the remodeling process characterized by increased wall lumen thickness and the reduced internal and external diameters. We showed that the association between aortic stiffness and M/L ratio was weakened, but remained statistically significant after controlling for age and mean arterial pressure, suggesting that cardiovascular risk factors may influence the development of vascular damage in both large and small arteries, but their effect does not completely explain this association.

The possible influence of the renin angiotensin aldosterone system or of glucose metabolism derangement was not confirmed by subgroup analysis. The association between increased PWV and M/L ratio was not statistically significant in patients with secondary hypertension or with type 2 diabetes mellitus, possibly, because the sample size was reduced in these subgroup analyses.

A causal relationship between large and small vessels disease cannot be extrapolated by our results. The decrease in aortic stiffness and the exposure of small vessels to highly pulsatile pressure and flow could stimulate small artery remodeling or, alternatively, higher mean BP, because of alterations in microvascular structure, could exert a load on nonmuscular components of the aortic wall increasing aortic stiffness.
In addition, microcirculation is not only the site of vascular resistance but also, probably, the origin of most of the wave reflections generating increased central SBP with aging.\(^5\) Although the proper location of a reflection site is elusive,\(^6\) the eutrophic or hypertrophic remodeling of small arteries could enhance the wave reflections and contribute, at least in part, to the amount of central pulse pressure because of the sum of incident and reflected waves.

Larger values of AI\(x\) could indicate increased wave reflection from the periphery or earlier return of the reflected wave as a result of increased PWV (attributable to increased arterial stiffness).

In our study, M/L ratio was significantly associated with greater AI\(x\) and lower pulse pressure amplification, both suggesting that a greater magnitude of reflected wave may affect central arteries during systole and not diastole. The relationship between M/L and AI\(x\) remained significant after adjustment for heart rate (a factor influencing the timing of the interaction of the incident pressure wave and wave reflection) and explained, although with a small contribution, the increase of AI\(x\), independently of BP.

Strengths of our study include the use of robust measures for aortic stiffness, that is, PWV, proposed as the gold standard for arterial stiffness measurement\(^22\) and for small resistance arteries, M/L ratio.\(^35\) We have studied quite a large number of individuals free of clinical cardiovascular disease with both essential and secondary hypertension and with different degrees of cardiovascular risk factors. However, the present study must be interpreted within the context of its potential limitations.

We cannot exclude that other reflection sites, located in larger arteries, have played a role in the mechanism of a disturbed wave reflection, although renal artery stenosis, calcified plaques in the carotids, and abdominal aortic aneurisms, had been excluded by ultrasound. In addition, small resistance arteries are only one part of the microcirculation and precapillary arterioles and capillaries structural and functional changes may also influence peripheral resistances.

Only one third of patients were naïve to antihypertensive treatment and we cannot exclude a possible effect of antihypertensive drugs on macro and microvasculature alterations. The effect of different classes of antihypertensive drugs seems to be similarly favorable or ineffective on both small resistance arteries and large arteries stiffness, thus not strongly altering the relationship between macro- and microvasculature.\(^36,37\)

**Perspectives**

It is well recognized that the development of vascular damage at both the macro- and microcirculatory levels is responsible for the occurrence of cardiovascular events. In this study,

### Table 3. Independent Predictors of Carotido-Femoral Pulse Wave Velocity in a Stepwise Multiple Linear Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized</th>
<th>Standardized</th>
<th>Unstandardized</th>
<th>Standardized</th>
<th>Unstandardized</th>
<th>Standardized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.105</td>
<td>0.016</td>
<td>0.549</td>
<td>&lt;0.0001</td>
<td>0.398</td>
<td>0.406</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>0.073</td>
<td>0.018</td>
<td>0.337</td>
<td>&lt;0.0001</td>
<td>0.541</td>
<td>0.148</td>
</tr>
<tr>
<td>Media/lumen ratio</td>
<td>24 010</td>
<td>11 030</td>
<td>0.185</td>
<td>0.033</td>
<td>0.564</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Only variables that entered the final model are reported.

### Table 4. Independent Predictors of Central Systolic Blood Pressure in a Stepwise Multiple Linear Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized</th>
<th>Standardized</th>
<th>Unstandardized</th>
<th>Standardized</th>
<th>Unstandardized</th>
<th>Standardized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotido-femoral pulse wave velocity</td>
<td>2.146</td>
<td>0.79</td>
<td>0.328</td>
<td>0.009</td>
<td>0.196</td>
<td>0.208</td>
</tr>
<tr>
<td>Media/lumen ratio</td>
<td>244.293</td>
<td>100.61</td>
<td>0.294</td>
<td>0.018</td>
<td>0.254</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Only variables that entered the final model are reported.

### Table 5. Independent Predictors of Augmentation Index in a Stepwise Multiple Linear Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized</th>
<th>Standardized</th>
<th>Unstandardized</th>
<th>Standardized</th>
<th>Unstandardized</th>
<th>Standardized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>0.413</td>
<td>0.072</td>
<td>0.501</td>
<td>&lt;0.0001</td>
<td>0.208</td>
<td>0.221</td>
</tr>
<tr>
<td>Height, cm</td>
<td>0.588</td>
<td>0.100</td>
<td>0.513</td>
<td>&lt;0.0001</td>
<td>0.389</td>
<td>0.188</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.163</td>
<td>0.051</td>
<td>0.298</td>
<td>0.002</td>
<td>0.519</td>
<td>0.108</td>
</tr>
<tr>
<td>Media/lumen ratio</td>
<td>96 240</td>
<td>42.523</td>
<td>0.207</td>
<td>0.031</td>
<td>0.549</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Only variables that entered the final model are reported.
a relationship between alterations in the microvasculature assessed by the M/L ratio in small resistance arteries and aortic stiffness was shown. In addition, small arteries remodeling may contribute, at least in part, to an increase in central pressure by increasing the magnitude of wave reflections. The relevant clinic impact of these observations relies in the possible prevention or regression of both vascular alterations.

Sources of Funding

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Disclosures

None.

References


**Novelty and Significance**

**What Is New?**

- The assessment of the relationship between aortic stiffness and small resistance arteries structural changes, assessed by the media/lumen ratio.

**What Is Relevant?**

- Abnormalities in small and large arteries are interrelated and may contribute to the development and progression of hypertensive disease and complications.

**Summary**

Alterations in the microvasculature are related to aortic stiffness and might contribute to the increase in central pressure. The possible prevention or regression of both vascular alterations could have relevant clinical impact.
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