Central Pulse Pressure Is an Independent Determinant of Vascular Remodeling in the Retinal Circulation

Christian Ott, Ulrike Raff, Joanna M. Harazny, Georg Michelson, Roland E. Schmieder

Abstract—Pulse pressure has been recognized as a risk factor for stroke. Moreover, it was shown that central pulse pressure relates more strongly to vascular disease and outcome than (peripheral) brachial pulse pressure. Because vascular remodeling in the retinal circulation mirrors the 1 in the cerebral circulation and represents an easy, noninvasive possibility to assess microvascular changes in humans, we analyzed the impact of central pulse pressure on retinal vascular structure in humans. The study cohort comprised 135 nondiabetic patients across a wide range of blood pressure values. Parameter of retinal arteriolar remodeling (wall-to-lumen ratio) was assessed noninvasively and in vivo by scanning laser Doppler flowmetry. Central pulse pressure and augmentation index normalized to a heart rate of 75 beats per minute were assessed by pulse wave analysis. Central pulse pressure correlated with wall-to-lumen ratio ($r=0.302; P<0.001$), central augmentation index normalized to a heart rate of 75 beats per minute correlated with wall-to-lumen ratio ($r=0.190; P=0.028$), and in accordance pulse pressure amplification (peripheral pulse pressure/central pulse pressure) was negatively correlated with wall-to-lumen ratio ($r=-0.223; P=0.009$). In contrast, central mean arterial pressure was not correlated with wall-to-lumen ratio ($r=0.110; P=0.203$). Multiple regression analysis revealed an independent relationship between wall-to-lumen ratio and central pulse pressure ($\beta=0.277; P=0.009$), but not with other classical cardiovascular risk factors. Thus, central pulse pressure, indicative of changes in large conduit arteries is an independent determinant of vascular remodeling in small retinal arterioles. Such a relationship indicates a coupling and crosstalk between the microvascular and macrovascular changes attributable to hypertension. (Hypertension. 2013;61:1340-1345.)

Key Words: arterioles ■ augmentation index ■ central pulse pressure ■ retinal circulation ■ wall-to-lumen ratio

Although the importance of hypertension as predictor of coronary heart disease and stroke has been known for a long time, the relative contribution of the individual components of peripheral blood pressure (BP) to the development of cardiovascular (CV) disease is still a matter of debate.\(^1\)\(^-\)\(^5\) More striking nowadays, the importance of central hemodynamics is more and more acknowledged. Pathophysiologically, it seems consistent that the estimation of the central pressure in the aorta, which is actually the perfusion pressure to key organs, rather than the pressure in the arm, provides more relevant prognostic information. Indeed, it has been shown in a population-based study (the Strong Heart Study)\(^6\) and in a hypertension trial (the Conduit Artery Function Evaluation [CAFÉ] study)\(^7\) that the noninvasively measured central BP is superior to brachial BP in predicting CV outcomes. In a comprehensive review, Laurent et al\(^8\) summarized the evidence that central pressure and pulse pressure (PP) are superior indicators of incident CV disease in a variety of prospective studies.

Vascular remodeling, characterized by an increased media-to-lumen ratio (M/L) of small resistance and large arteries, has been identified as one of the early processes that occurs in response to increased BP and leads to hypertensive end-organ damage.\(^9\)\(^,\)\(^10\) The prognostic role of structural alterations of isolated subcutaneous small arteries and arterioles has been shown in arterial hypertension, with adverse prognosis in those patients with an increased M/L.\(^11\)\(^,\)\(^12\) Moreover, in a former study it was shown that, although all known CV risk factors were considered, only PP and M/L were significantly associated with the occurrence of CV events.\(^11\)

However, the evaluation of small artery and arteriolar structure of isolated subcutaneous small vessels requires an invasive procedure, namely the performance of a biopsy of subcutaneous tissue. Hence, this methodology is inadequate for routine patient management. In contrast, the analysis of the retinal vessels offers the opportunity to visualize the microvasculature of the body noninvasively, repeatedly, and safely in vivo. Hence, a new approach focuses on retinal arteriolar structural parameters by using scanning laser Doppler flowmetry (SLDF).

Previously, both methodologies SLDF (in vivo) and myograph (in vitro) were assessed in patients with hypertension and normotensive controls. A close correlation was observed between M/L of subcutaneous small arteries and wall-to-lumen ratio (WLR) of retinal arteries, indicating that SLDF may provide similar information about microvascular morphology compared with an invasive, accurate, and prognostically

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From the Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Germany (C.O., U.R., J.M.H., R.E.S.); and Department of Ophthalmology, University of Erlangen-Nuremberg, Germany (G.M.).
Correspondence to Roland E. Schmieder, Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Ulmenweg 18, 91054 Erlangen, Germany. E-mail roland.schmieder@uk-erlangen.de
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relevant micromyographic measurement of M/L of subcutaneous small arteries.\textsuperscript{15}

The relationship between the vascular remodeling of the large conduit arteries and the small resistance arteries in hypertension has not yet thoroughly been analyzed in humans, although a relationship between the macrocirculation and microcirculation is obvious. Hence, we analyzed in the current observational study the association and relationship of central pulse PP (a parameter of macrocirculation) with retinal arteriolar structure (microcirculation), mirroring cerebral circulation in subjects with a wide range of BP values.

Methods

Study Population

This observational study (n=135) was performed in our Clinical Research Unit of the Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Germany.

Subjects were recruited by advertising in local newspapers in the area of Erlangen-Nuremberg, Germany, and eligible subjects were enrolled consecutively. Written informed consent was obtained before study inclusion. Patients, aged 18 to 70 years, on antihypertensive and lipid-lowering drugs were asked to undergo a wash-out phase before assessment of baseline data.

Main exclusion criteria were secondary arterial hypertension, arterial hypertension grade 3, history or any present clinical evidence or CV or cerebrovascular disease, atrial fibrillation, estimated glomerular filtration rate <45 mL/min per 1.73m\(^2\) (using the Modification of Diet in Renal disease formula),\textsuperscript{14} diabetes mellitus (defined by fasting glucose \(\geq 7.0\) mmol/L, or on glucose-lowering medication), hepatic or hematologic disease, known epileptic disease, any significant eye disease, and smoking.

The study protocol was approved by the Local Ethics Committee (University of Erlangen-Nuremberg), and the study was conducted in accordance with the Declaration of Helsinki and the principles of good clinical practice guidelines.

Blood Pressure Measurements

Office BP was measured noninvasively in a sitting position after \(\geq\)15 minutes of rest using an oscillometric device (Dinamap Pro 100V2, Criticon, Norderstedt, Germany) with an appropriate cuff size. Average of 3 measurements at intervals of 2 minutes was calculated for analyses.

Assessment of Parameters of Retinal Arteriolar Remodeling

To assess the vascular structure (WLR) of retinal vessels, reflecting cerebrovascular circulation, SLDF at 670 nm (Heidelberg Retina Flowmeter, Heidelberg Engineering, Germany) was performed. No dilution of the pupil is required to perform the measurements using SLDF.

Measurement of Retinal Capillary Blood Flow

Retinal capillary blood flow was assessed using SLDF as previously described.\textsuperscript{15} Briefly, a retinal sample of 2.56x0.64x0.30 mm was scanned within 2 seconds at a resolution of 256 points \(\times\) 64 lines \(\times\) 128 lines. A specific length of the arteriole, reflecting arteriolar structure during 1 heart beat (1 systole and 1 diastole), was used for analyses, and the diameters were assessed every 10 \(\mu\)m of this specific length of the arteriole; the mean of measured diameters was finally considered for analyses. Analyses of the diameters were performed offline with automatic full-field perfusion imaging analysis. Outer diameter was measured in reflection images, and lumen diameter was measured in perfusion images. WLR was calculated using the formula (outer diameter–lumen diameter)/lumen diameter. Measurements were performed by 1 of 4 experienced research nurses extensively trained in this kind of analysis. In addition, all images were approved by a scientist who is one of the leading persons in developing and establishing this method, with \(\geq\)15 years of experience. The scientist was blinded to the clinical characteristics of patients. Using the new software version (SLDF 4.0), we previously showed that the intraobserver and interobserver reproducibility was \(<10\%\).\textsuperscript{16}

Pulse Wave Analysis

All subjects were studied in sitting position in a quiet and temperature-controlled room. Brachial BP was measured on the dominant arm with an oscillometric device (Dinamap Pro 100V2; Criticon, Norderstedt, Germany), and averages of the last 3 measurements were taken. Immediately thereafter, radial artery waveforms were sampled in the same arm by noninvasive technique, calibrated to the brachial mean arterial pressure and diastolic BP, with the commercially available SphygmoCor System (AtCor Medical, Sydney, Australia). In brief, radial artery waveforms were recorded from the radial artery at the gently hyperextended wrist, using high-fidelity applanation tonometer (Millar Instruments, Houston, Tex.), directly into the SphygmoCor System. Radial artery waveform was averaged from single waveforms recorded consecutively for 10 seconds. Corresponding central (aortic) waveforms were then automatically generated from the radial artery waveform by a validated transfer function.\textsuperscript{18–20} From the derived central waveforms, data are given for central systolic, diastolic BP, central PP, augmentation pressure as the pressure height difference between the second and the first systolic peaks and the central augmentation index (central AIx) defined as the pressure difference between these peaks, expressed as percentage of central PP. The central AIx is also given normalized to a heart rate of 75 beats per minute (central AIx@75). Duplicate recordings included in the analysis had high quality, defined as in-device quality index \(\geq 80\%\) (as derived from an algorithm that includes average pulse height, pulse height variations, diastolic variations, and the maximum rate of rise of the peripheral waveform). PP amplification is determined as the ratio of peripheral PP to central PP.

Statistical Analyses

Normal distribution of data was confirmed by Kolmogorov–Smirnov tests before further analysis. Using this test, all parameters were found to reveal a normal distribution. Data are given as mean\(\pm\)SD. Univariate correlation was performed using Pearson correlation coefficient. Multiple linear regression analyses were performed to determine whether individual components of BP were independent of possible confounders related to the WLR. Only 1 parameter per variable group (eg, low-density lipoprotein-cholesterol in the lipid variable group) was eligible to be entered as an independent variable, aiming to avoid statistical error attributable to collinearity. The independent variables were entered simultaneously (multiple linear regression, enter procedure). Two-tailed values of \(P<0.05\) were considered statistically significant. All analyses were performed using IBM SPSS Statistics 19 (SPSS Inc, Chicago, IL).
Results

The study cohort comprised 135 middle-aged patients across a wide range of BP values, without evidence of diabetes mellitus. Patient characteristics are given in Table 1.

A detailed correlation analysis between WLR of retinal arterioles and both peripheral and central hemodynamics is depicted in Table 2. Both peripheral and central systolic BP as well as PP correlated with WLR, but central PP showed the strongest correlation (Table 2; Figure 1). In contrast, peripheral and central diastolic BP as well as mean arterial pressure were not correlated with WLR. In accordance, PP amplification was negatively correlated with WLR (Table 2; Figure 2).

To determine further univariate predictors of WLR of retinal arterioles, we performed correlation analyses between various CV risk factors and WLR. Age revealed a positive correlation with WLR ($r=0.208; P=0.016$), but neither body mass index ($r=0.085; P=0.324$), fasting glucose ($r=-0.020; P=0.821$), low-density lipoprotein-cholesterol ($r=-0.125; P=0.152$), nor serum creatinine ($r=0.002; P=0.984$), and estimated glomerular filtration rate ($r=-0.130; P=0.137$), respectively, were correlated with WLR.

Baseline retinal capillary blood flow was negatively correlated with WLR ($r=-0.189; P=0.029$), that is, the more advanced vascular remodeling of the retinal arteriole the more reduced retinal capillary perfusion.

Multiple regression analyses were performed to assess the quantitative impact of central vascular parameters and various CV risk factors on WLR. Both central (Model 1) and peripheral PP (Model 2) were the only independently related determinants of WLR of retinal arterioles (Table 3). None of the other individual components of peripheral or central hemodynamics (systolic, diastolic BP, and mean arterial pressure) revealed such a strong positive and independent relationship to WLR (data not shown). Finally, there was no difference whether the classical CV risk factors were entered as independent variables in the multivariate model or not.

Discussion

CV risk scores are quite effective in predicting CV events in patients with high total CV risk. However, these risk scores may underestimate the risk of CV events in other risk groups with a moderate CV risk suitable for early prevention. Hence, additional (bio-) markers for the prediction of the individual risk have been intensively investigated. It was proposed that parameters of target-organ damage can be used as tissue biomarkers together with (or preferentially independently of) classical CV risk factors, identifying patients at high risk of developing CV disease.

Within this context, markers of increased arterial stiffness of large conduit arteries and central PP have gained increasing interest. Arterial stiffness and wave reflection are now well accepted as the most important determinants of increasing systolic and PP in patients with CV risk. Pathophysiology of arterial stiffening and an increased amplitude of wave reflections attributable to peripheral vasoconstriction lead to an

Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45.7±13</td>
</tr>
<tr>
<td>Sex, m/w</td>
<td>120/15</td>
</tr>
<tr>
<td>Height, cm</td>
<td>179±9</td>
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<tr>
<td>Weight, kg</td>
<td>85.9±15</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.7±4.0</td>
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<tr>
<td>Office systolic BP, mmHg</td>
<td>135±16</td>
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<tr>
<td>Office diastolic BP, mmHg</td>
<td>83±12</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.22±0.7</td>
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<tr>
<td>Triglyceride, mmol/L</td>
<td>1.95±1.4</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.72±1.2</td>
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<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>3.73±0.9</td>
</tr>
<tr>
<td>Serum creatinine, µmol/L</td>
<td>77.8±8.8</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure; and LDL, low-density lipoprotein.

Table 2. Correlation Analysis Between WLR and Both Peripheral and Central Hemodynamics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$R$</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral</td>
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<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>0.212</td>
<td>0.014</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>−0.024</td>
<td>0.786</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>0.110</td>
<td>0.203</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>0.270</td>
<td>0.002</td>
</tr>
<tr>
<td>Central</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>0.270</td>
<td>0.011</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>−0.025</td>
<td>0.775</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>0.110</td>
<td>0.203</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>0.302</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral/central</td>
<td>−0.223</td>
<td>0.009</td>
</tr>
<tr>
<td>PP amplification</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP indicates blood pressure; MAP, mean arterial pressure; PP, pulse pressure; and WLR, wall-to-lumen ratio.

Figure 1. Correlation between wall-to-lumen ratio (WLR) of retinal arterioles and central pulse pressure.
earlier return and a higher amplitude of arterial wave reflections in the aorta. This results in an inadequate increase in systolic BP and a relative decrease in diastolic BP, thus increasing central PP at any given value of mean arterial pressure. Central PP has been shown to be a predictor of all CV events and CV as well as all-cause mortality. Moreover, a higher central PP is associated with an increase in carotid wall thickness and cerebral white matter lesions. Because of the common origin from the internal carotid artery, both cerebral and retinal vessels share similar morphological and functional properties. Studies on retinal circulation, using SLDF, therefore might be regarded as useful alternatives, easily accessible and noninvasively measurable, to provide valuable insights of the cerebral circulation. Most recently a close relation between remodeling of small arteries assessed in vitro from biopsies was found to be related to changes to retinal arteriolar changes (ie, WLR) measured by SLDF.

Indeed, by using SLDF, we could show that WLR of retinal arterioles is increased in patients with hypertension and cerebrovascular events compared with treated hypertensives and normotensives. Moreover, we have shown that WLR seems to be a robust indicator of the severity of hypertension, the presence of early renal damage, and, in contrast with arteriolar-to-venular ratio, is related to the extent of atherosclerotic damage in the carotid artery, as indicated by evaluation of the intima-media thickness.

Hence, the major and novel finding of this observational study is that central PP is a strong and an independent predictor of vascular remodeling (WLR) in the retinal circulation beyond classical CV risk factors and additional factors that are proposed to have an impact on vascular structure. Our findings support the concept that changes in the macrovasculature (central PP) and microvasculature (WLR) are deeply interrelated, following a vicious circle. Microvascular structural alterations (eg, increased WLR) are a major factor for an increase in mean BP, which, in turn, increases shear stress and hence arterial stiffness of large arteries, indicated by an increased PP. Hence, increased pulsatile pressure subsequently damages small arterioles, that is, induces and aggravates microvascular damage.

Central AIx, a direct measure of pulse wave reflection, was shown to independently predict both the premature coronary artery disease and an increased risk for severe short-term and long-term CV events in patients undergoing percutaneous coronary intervention. In our study, central AIx correlated with WLR. It is well known that age-related changes of central AIx are nonlinear, increasing more in younger (<50 years) individuals, suggesting that central AIx might be a more sensitive marker of arterial stiffening in the younger patients. The mean age in our study cohort was about 46 years, meaning that many patients were in the range and above the age, when AIx might lose its sensitivity. This might in part explain that regression analysis revealed that age is not an independent determinant of WLR.

The augmentation of central systolic BP and PP, as a consequence of increased arterial stiffness and wave reflection, is associated with loss of PP amplification, meaning that the central and the peripheral PP become more similar. The disappearance of PP amplification after 54 months of follow-up was a strong independent predictor of all-cause and CV mortality in patients with end-stage renal disease. In accordance, in our observational study, PP amplification was negatively correlated with WLR of retinal arterioles, but did not emerge as an independent determinant of WLR in the multiple regression analysis.

Previously, it has been shown that M/L of subcutaneous small arteries was related among others to pulse wave velocity...
in 73 patients with essential and secondary hypertension with or without diabetes mellitus.33

Concerns have been raised about the limitation of an in-built transfer function for estimation of central hemodynamics from radial waveform. It has to be kept in mind that the use of a transfer function is an approximation, which however was repeatedly shown to be an accurate method for estimation of central hemodynamics.18–20 Additionally, in a former study, we could also show both an excellent agreement of the absolute values (137±27 mmHg vs 136±23 mmHg), for example, no shift of baseline values with SphygmoCor, and a high correlation (r=0.860; P<0.001) between invasively and noninvasively assessed central systolic BP by SphygmoCor.34

Our study cohort comprised a wide range of BP values, including patients who were normotensive. Recently, in the Japan Public Health Center–based prospective (JPHC) study, it was found that PP is an independent risk factor for stroke among middle-aged patients who were normotensive, suggesting that PP may be useful to predict the risk of stroke in these patients. Hence, it was suggested that pulsatile load even with normal steady state load may eventually lead to elevated risk of stroke.35 This study is remarkable because it underscores the importance of the pulsatile component of organ perfusion and illustrates the interrelationship between microcirculation and macrocirculation.

Perspectives
We found that central PP, indicative of changes in large conduit arteries, is an independent determinant of remodeling in small retinal arterioles. Such a relationship indicates a coupling and crosstalk between the microvascular and macrovascular changes attributable to hypertension. Previously, in an editorial comment it was stated “If we are to move beyond brachial BP measurement for the assessment of circulatory pressures and function in routing clinical practice, the most logical target for future studies is the noninvasive assessment of central aortic pressures and/or pulse wave velocity.”27,28 Hopefully, we can expand this notion to determination of individual CV risk by including the assessment of retinal arteriolar structure, which is possible noninvasively, repeatedly, safely, and in vivo.

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Disclosures
None.

References
Novelty and Significance

What Is New?
- Central pulse pressure is a strong and independent predictor of vascular remodeling (wall-to-lumen ratio) in the retinal circulation beyond classical cardiovascular risk factors and additional factors that are proposed to have an impact on vascular structure.
- Such a relationship indicates a coupling and crosstalk between the microvascular and macrovascular changes attributable to hypertension.

What Is Relevant?
- Assessment of wall-to-lumen ratio represents an easy, noninvasive possibility to assess microvascular changes in humans and might represent an interesting research and potentially clinical tool to assess the individual cardiovascular risk in vivo.

Summary
We found that central pulse pressure, indicative of changes in large conduit arteries, is an independent determinant of remodeling in small retinal arterioles. Such a relationship indicates a coupling and crosstalk between the microvascular and macrovascular changes attributable to hypertension.
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