Cerebral Vasomotor Reactivity and Extent of White Matter Lesions in Middle-Aged Men With Arterial Hypertension: A Pilot Study

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BACKGROUND
Cerebrovascular reactivity (CVR) impairment and cerebral white matter lesions (WMLs) are associated in elderly or patients with overt cerebral ischemia. Such association has not been confirmed for asymptomatic middle-aged individuals with risk factors for stroke. We assessed the relationship between the CVR and the presence of WMLs in a middle-aged population-based cohort of hypertensive men.

METHODS
Magnetic resonance imaging (MRI) and transcranial Doppler (TCD) examination were performed in 54 hypertensive men, all at 60 years of age, without a history of stroke, neurologic deficits, or carotid stenosis. The CVR of the middle cerebral artery (MCA) was expressed as the vasomotor reactivity reserve (VMRr).

RESULTS
WMLs were detected in 22 men (40.7%); all WMLs were classified as mild (first grade of the Fazekas modified scale). The VMRr was lower in patients with WMLs (mean 55%; s.e. 3%) compared to those without WMLs (mean 65%; s.e. 3%; P = 0.03). The lower VMR in patients with WMLs was consistent after controlling for confounders. A higher pulsatility index (PI) in subjects with WMLs (mean 1.08; s.e. 0.05) compared to those without WMLs (mean 0.90; s.e. 0.05; P = 0.01) was not consistent after controlling for confounders.

CONCLUSIONS
The CVR was lower in middle-aged hypertensive men with WMLs compared to those without WMLs indicating that even a low load of WMLs may reflect some functional impairment of the cerebral microvasculature.

Keywords: arterial hypertension; blood pressure; hypertension; transcranial Doppler; vasomotor reactivity; white matter lesions

Vasomotor reactivity testing with transcranial Doppler (TCD) is commonly used to measure cerebrovascular reactivity (CVR), which serves as a marker of cerebral microcirculation function.1,2 The CVR of the middle cerebral artery (MCA) territory is usually impaired ipsilaterally in patients with symptomatic or asymptomatic high-grade carotid artery stenosis or vessel occlusion, as a result of chronic dilatation of resistance vessels due to chronic hypoperfusion.1,3 Impairment of CVR exists in symptomatic and asymptomatic patients with cerebral microangiopathy.4,5 In hypertensive patients, CVR is negatively correlated with patient age and the duration of hypertension, and reduced CVR is associated with a history of cerebrovascular events.6,7 Cerebral white matter lesions (WMLs) represent deep and subcortical white matter damage of vascular origin that can be detected on magnetic resonance imaging (MRI) in the elderly, as well as in the younger population with arterial hypertension.8,9 The WML load is mostly related to patient age and the course of arterial hypertension.10–12 However, the presence of WMLs in the elderly is associated with an increased risk of stroke independent of other stroke risk factors.13 Impairment of CVR has been shown in elderly subjects with a high load of clinically asymptomatic WMLs when compared to those without WMLs.14,15 In contrast, such a relationship was not confirmed for middle-aged, asymptomatic patients with arterial hypertension.16,17 Therefore, it remains uncertain whether CVR is only impaired in more advanced stages of cerebral microangiopathy or if these alterations also occur in earlier disease stages. To answer this question, it seems reasonable to assess CVR in a group of middle-aged men.
hypertensive subjects without symptomatic cerebral ischemia because hypertension is the most relevant risk factor for the development of cerebral microangiopathy and WMLs.

Thus, the goal of our study was to verify the hypothesis of an association between altered cerebral vessel reactivity and WMLs in a population-based cohort of middle-aged asymptomatic men after controlling for blood pressure values, type 2 diabetes mellitus (DM2), and cigarette smoking.

METHODS

Study population. The study was part of a primary prevention program for arterial hypertension, diabetes mellitus, and lipid abnormalities (SOPKARD), which was performed in the town of Sopot in Poland (40,000 inhabitants). On study entry, all inhabitants of Sopot at 60 years of age were invited for two screening examinations: the first performed by trained nurses and the second performed by trained general practitioners within 7 days from the first examination. Each visit included four blood pressure measurements: three on the dominant and one on the opposite arm.

Four hundred thirty-nine persons responded to the invitation (274 women and 191 men). Sixty-nine men were deemed to be hypertensive, free from prior cardiovascular events (myocardial infarction, transient ischemic attack, or stroke), symptomatic peripheral artery disease, carotid artery stenosis (>50%), and focal deficits on neurologic examination. Eight of the 69 men were excluded for the following reasons: severe chronic respiratory disease (n = 1), chronic alcohol abuse (n = 2), atrial fibrillation (n = 2), or normotension (n = 3). Furthermore, seven men were excluded because of contraindications for TCD (inappropriate temporal bone window, n = 3) or MRI (n = 4). Fifty-four hypertensive men, all at 60 years of age, were therefore included in the study. Two patients (3.7%) revealed asymptomatic cerebral infarctions in the cortical regions on MRI, and were therefore excluded from any analysis. Among the remaining 52 men, 26 (50%) received antihypertensive therapy before study entry and 16 (30.8%) had DM2.

The study protocol was approved by the Medical Ethics Committee of the Medical University of Gdańsk (NKEBN/437/2002/2004). All participants signed an informed consent.

Subject characteristics. Information on the patient’s medical history, addictions, and medical treatments were obtained by a standardized face-to-face interview. The weight and height were recorded and expressed as the body mass index. A certified neurologist performed a standardized neurologic examination.

Hypertension was defined according to the JNC 7 (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) criteria. Additionally, fundoscopy was performed by a certified ophthalmologist in newly diagnosed subjects. Those without signs of hypertensive retinopathy were considered normotensive and were therefore excluded from the study. DM2 was considered to be present if diagnosed previously by a physician, or if two random glucose readings exceeded 200 mg/dl or one fasting blood glucose reading exceeded 125 mg/dl. Hyperlipidemia was defined as a total serum cholesterol level >200 mg/dl (>175 mg/dl for DM2 patients) or current statin use. Cigarette smoking was categorized as currently active or stopped within 2 years prior to the examination.

24-h Ambulatory blood pressure monitoring. The 24-h ambulatory blood pressure monitoring was performed in each study participant on the day before the cerebral vessel reactivity testing. ABP monitor (model 90207; SpaceLabs Healthcare, Issaquah, WA) was fitted to the nondominant arm. Measures were obtained every 20 min during the daytime (8 AM to 10 PM) and every 30 min during the night time (midnight to 6 AM). Transitional periods from 6 AM to 8 AM and 10 PM to midnight were not included in the analyses. Adequacy of recordings was based on acceptable readings: at least 90% of measurements were required for the test to be considered technically successful. Patients with systolic blood pressure day-to-night reduction <10% were considered as nondippers.

TCD examination. All ultrasound examinations were performed under standardized conditions. The ultrasound examinations were performed in the same place and at the same time of the day (between 10 AM and 2 PM). Participants were instructed not to drink coffee or smoke cigarettes within 12 h before the examination, to avoid sleep deprivation, and to eat normal meals the day before the examination.

On study entrance, all of the participants were screened for carotid artery stenosis with carotid duplex ultrasonography (Aloka 5000 device with a linear 5–10 MHz probe; Aloka, Tokyo, Japan) and for possible cardiac sources of brain embolization with echocardiography (Aloka 5000 device with a 2–2.5 MHz sector probe).

The MCAs were examined with TCD through the temporal bone window using a MultiDop T2 DWL device (DWL Elektronische Systeme, Singen, Germany), equipped with a 2 MHz PW, handheld transducer by one, well-trained ultrasonographer (G.M.K.).

The mean blood flow velocity at baseline (rest $V_{mean}$) and pulsatility index (PI) were recorded in both MCAs. The mean values of the arithmetical means of rest $V_{mean}$ and PI measured in both MCAs were used for further analyses. Subsequently, ventilation tests were performed for provoking changes in the partial concentration of carbon dioxide. Vasomotor reactivity was assessed in the randomly selected MCA: 20 on the left and 32 on the right side. Baseline blood flow velocity (base $V_{mean}$) was recorded after 10 min of rest in supine position. Minimal value of mean blood flow velocity (min $V_{mean}$) was recorded at hypocapnia, at the end of 2 min of hyperventilation. Maximal value of mean blood flow velocity (max $V_{mean}$) was recorded at hypercapnia, immediately after 30 s of breath-holding. End-tidal CO₂ concentrations were monitored continuously during the entire procedure using capnograph (Normocap; Datex, Helsinki, Finland). Systemic blood pressure and heart rate were measured before and after the tests. Recording analyses...
and velocity measurements were done manually, offline, using the monitoring program (MF version 8.27; DWL Elektronische Systeme). The vasomotor reactivity reserve (VMRr), expressed as the percentage change in mean blood flow velocity from hypo- to hypercapnia, was calculated from $100 \times (\text{max } V_{\text{mean}} - \text{min } V_{\text{mean}})/\text{base } V_{\text{mean}}$ according to the protocol described by Markus and Harrison.19,20

Reproducibility measurements of VMRr were performed in a sample of 10 individuals. The intraclass correlation coefficient for two consecutive measurements was 0.91 ($P < 0.01$).

**MRI.** MRI was performed using a Picker 1.5 Tesla scanner (Picker International, Cleveland, OH) with 5 mm transverse slices. All scans were read by one well-trained neuroradiologist (M.D.), who was blinded to the patient's identity and history. WMLs were defined as areas of hyperintensity on proton-density and T2-weighted images without prominent hypointensity on T1-weighted scans.21 The load of the WML was graded with the Fazekas modified scale.22 Asymptomatic cortical infarcts were defined as hyperintensive gray matter lesions on T2-weighted or FLAIR (fluid attenuated inversion recovery) images (at least 3 mm in diameter on any plane) with a cortical distribution in the MCA territory.23 The interval between the MRI and ultrasound examination did not exceed 48 h.

**Statistics.** Univariate analyses were performed with STATISTICA, version 7.1 (StatSoft, Tulsa, OK). The Shapiro–Wilk test was performed to analyze the distribution of linear variables. Differences between groups were analyzed with Student's $t$-test in the case of normally distributed variables (VMRr, PI, and flow measurements) or with the Mann–Whitney test in the case of non-normally distributed variables (end-tidal CO$_2$, duration of arterial hypertension (years), and body mass index). The $\chi^2$ test was used to compare categorized variables such as DM2, hyperlipidemia, cigarette smoking, nocturnal blood pressure dipping, and treatment with antihypertensive drugs or statins between different groups. In case the number of patients per group was <10, Yates correction was used. Several fixed-effects one-way analysis of covariance (ANCOVA) models were calculated to compare mean VMRr and PI between subjects with and without WML after controlling for DM2, antihypertensive drug use, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, statin use, and obesity. ANCOVA was calculated with SAS 9.1 (SAS Institute, Cary, NC) using the PROC generalized linear model analysis. Adjusted mean values were calculated as least squares means and reported together with standard error of the mean. $P$ values were computed with the least significant difference approach. A $P < 0.05$ was regarded as statistically significant.

**RESULTS**

Generalized linear model power procedure, with VMRr as dependent and presence of WMLs as independent variable, showed power value of 0.52 (52 observations, $\alpha = 0.05$ and s.e. 0.17). Generalized linear model power procedure, with PI as dependent and presence of WMLs as independent variable, showed power value of 0.69 (52 observations, $\alpha = 0.05$ and s.e. 0.25).

Of the 52 hypertensive men in the current study, 22 (42.3%) had WMLs on MRI, which were located in the periventricular white matter in 14 subjects (26.9%) and the subcortical white matter in 8 subjects (15.4%). All WMLs were classified as mild (first grade on the Fazekas modified scale, which is defined as a single lesion $<10$ mm in diameter or areas of grouped lesions $<20$ mm in any diameter). We found no differences in the clinical characteristics between the subjects with and without WMLs (Table 1).

The VMRr was lower and mean PI was higher in men with WMLs compared to those without WMLs (Figures 1 and 2). No differences between the groups existed regarding mean flow velocities at rest (48.5 (s.d. $\pm$ 7.0 cm/s) vs. 48.8 (s.d. $\pm$ 9.6 cm/s);

![Table 1 | Baseline characteristics of subjects with and without WMLs on MRI](https://academic.oup.com/ajh/article-abstract/23/11/1198/198072)

<table>
<thead>
<tr>
<th>Type 2 diabetes mellitus (n, % of patients)</th>
<th>WML positive patients, $n = 22$</th>
<th>WML negative patients, $n = 30$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia, total cholesterol $&gt;200$ mg/dl ($&gt;175$ mg/dl for DM2 patients) or current statin use (n, % of patients)</td>
<td>17 (77.2%)</td>
<td>25 (83.3%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Cigarette smoking (n, % of patients)</td>
<td>8 (36.4%)</td>
<td>12 (40.0%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Median of BMI (kg/m$^2$) ($\mu$)</td>
<td>27.75 (22.2–38.6)</td>
<td>25.9 (20.3–32.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean of ABPM systolic blood pressure (mm Hg), s.d.</td>
<td>133 $\pm$ 9</td>
<td>127 $\pm$ 13</td>
<td>0.13</td>
</tr>
<tr>
<td>Mean of ABPM diastolic blood pressure (mm Hg), s.d.</td>
<td>81 $\pm$ 8</td>
<td>79 $\pm$ 8</td>
<td>0.51</td>
</tr>
<tr>
<td>Diurnal variation of ABPM (n, % of nondippers)</td>
<td>10 (45.5%)</td>
<td>15 (50%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Median of duration of arterial hypertension (years) ($\mu$)</td>
<td>5 (1–9)</td>
<td>4.5 (1–20)</td>
<td>0.70</td>
</tr>
<tr>
<td>Antihypertensive treatment (n, % of patients)</td>
<td>12 (54.5%)</td>
<td>14 (46.7%)</td>
<td>0.57</td>
</tr>
<tr>
<td>ACEI or ARB treatment (n, % of patients)</td>
<td>10 (45.4%)</td>
<td>7 (23.3%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Statin treatment (n, % of patients)</td>
<td>4 (18.2%)</td>
<td>9 (30.0%)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Table 1 | Baseline characteristics of subjects with and without WMLs on MRI

ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DM2, type 2 diabetes mellitus; MRI, magnetic resonance imaging; $\mu$, min to max; WMLs, white matter lesions.
P = 0.89), the median end-tidal CO₂ concentrations after hyperventilation (3.0 (range, 2.0–4.0%) vs. 3.0 (range, 2.0–4.0%); P = 0.78) or after breath-holding (5.0 (range, 3.8–6.5%) vs. 5.5 (range, 3.8–6.5%); P = 0.08).

In spite of a difference of borderline significance regarding PI in patients with WMLs and DM2, we found no significant differences regarding VMRr or PI values between the subgroups of patients with WMLs distinguished on the basis of the presence of concomitant vascular risk factors (Table 2).

In unadjusted ANCOVA models, the mean VMRr was significantly lower (55%; s.e. 0.03 vs. 65%; s.e. 0.03; P < 0.05) and the mean PI was significantly higher (1.08; s.e. 0.05 vs. 0.90 s.e. 0.05; P < 0.05) in subjects with WML than in those without WML. After adjustment for DM2, these differences remained statistically significant. In an ANCOVA model adjusted for DM2, antihypertensive treatment, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, statin use, and obesity, differences in mean PI between subjects with and without WML were no longer statistically significant (1.08; s.e. 0.06 vs. 0.96; s.e. 0.06; P = 0.08; Figure 2), whereas DM2 had a significant effect on mean VMRr (P < 0.01).

DISCUSSION

This study demonstrated that the CVR is lower in middle-aged hypertensive men with a low load of WMLs compared to those without WMLs, whereas both groups did not significantly differ with respect to vascular risk factors,

![Figure 1](https://academic.oup.com/ajh/article-abstract/23/11/1198/198072)

![Figure 2](https://academic.oup.com/ajh/article-abstract/23/11/1198/198072)

**Figure 1** | Mean vasomotor reactivity reserve (VMRr) in subjects with and without WMLs on magnetic resonance imaging. Adjusted mean values were calculated in different analysis of covariance models as least squares means and reported together with standard error of the mean (± s.e.m.); P values were computed with the least significant difference approach. Mean VMRr was determined in an unadjusted model, and after controlling for type 2 diabetes mellitus (DM2), and in a fully adjusted model controlling for DM2, obesity, statin, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use and antihypertensive treatment. WMLs, white matter lesions.

**Figure 2** | Mean pulsatility indexes (PIs) in subjects with and without WMLs. Adjusted mean values were calculated in different analysis of covariance models as least squares means and reported together with standard error of the mean (± s.e.m.); P values were computed with the least significant difference approach. Mean PI was determined in an unadjusted model, and after controlling for type 2 diabetes mellitus (DM2), and in a fully adjusted model controlling for DM2, obesity, statin and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use and antihypertensive treatment. WMLs, white matter lesions.

| Table 2 | Mean VMRr and PI values in subgroups of patients with WMLs distinguished on the basis of concomitant vascular risk factors |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | VMRr (%) s.d. P | PI s.d. P        |                 |                 |
| **Cigarette smoking, n = 8** |                 |                 |                 |                 |
| Present          | 48.7 ± 10.1     | 58.1 ± 13.0     | 0.09            | 1.03 ± 0.24     | 1.1 ± 0.32      | 0.63 |
| Absent           | 54.2 ± 14.9     | 55.5 ± 9.1      | 0.80            | 0.97 ± 0.20     | 1.23 ± 0.34     | 0.06 |
| **Type 2 diabetes mellitus, n = 9** |                 |                 |                 |                 |
| Present          | 54.2 ± 14.9     | 55.5 ± 9.1      | 0.80            | 0.97 ± 0.20     | 1.23 ± 0.34     | 0.06 |
| Absent           | 51.2 ± 7.2      | 54.4 ± 13.2     | 0.65            | 1.22 ± 0.41     | 1.04 ± 0.27     | 0.28 |
| **Hyperlipidemia, n = 17** | total cholesterol >200 mg/dL (>175 mg/dL for DM2 patients) or current statin use |                 |                 |                 |
| Present          | 51.2 ± 7.2      | 54.4 ± 13.2     | 0.65            | 1.22 ± 0.41     | 1.04 ± 0.27     | 0.28 |
| Absent           | 52.5 ± 14.8     | 61.9 ± 15.6     | 0.06            | 0.93 ± 0.22     | 0.99 ± 0.26     | 0.52 |

BMI, body mass index; DM2, type 2 diabetes mellitus; PI, pulsatility index; VMRr, vasomotor reactivity reserve; WMLs, white matter lesions.
antihypertensive agents, and statin treatment or duration of arterial hypertension. A higher PI in subjects with WMLs was not consistent after controlling for confounders.

Our results are in agreement with a previous study that reported lower CVR associated with symptoms of leukoaraiosis.24 Our results are also in agreement with studies that reported a significantly higher unadjusted cerebral vessel PI in the presence of WMLs in hypertensive humans, as well as in subjects with signs of diffuse small-vessel disease on MRI.14,25 Our data confirm studies that have reported an inverse association between WMLs and CVR in an asymptomatic elderly population with a high WML load (i.e., up to grade 3 on the Fazekas modified scale).14,15 The ratio of patients with WMLs in the study group was also similar to the ratio previously reported for this age-group of hypertensive individuals.9 However, in contrast to these reports, we have shown for the first time that CVR is also lowered in middle-aged clinically asymptomatic hypertensive subjects with very early stages of WMLs. This extends our knowledge about the mechanism and extent of asymptomatic cerebral ischemia in this age-group. Two recent studies did not demonstrate a relationship between CVR and WMLs in middle-aged individuals without clinical symptoms of cerebral ischemia.16,17 Differences in methodology of CVR testing used in the above-mentioned studies, a less homogeneous study population, and a smaller sample size of subjects with WMLs may have contributed to the lack of an association between CVR and WMLs.

The potential for type DM2 as a VMRr confounder has not been confirmed in our study. It stays in line with a previous study of van Oers et al.26 However, as it was previously reported, we found confounding effect of DM2 on PI.4,27 Because all obese patients were WMLs positive, we cannot exclude a confounding effect of body mass index on VMRr.

The higher sensitivity of the methodology of VMR testing in our study may partially explain the difference between our results and previously reported results. Pretnar-Oblak et al.17 and Sierra et al.16 evaluated NO- or CO2-induced vasodilatation. We measured the full range of vasodilatation induced by a combination of hypocapnic and hypercapnic tests. This approach seems to be more sensitive for the detection of early alterations of vasomotor reactivity than the use of a hypercapnic test alone.5 It probably explains why the latter showed a significant lowering of VMRr in spite of VMRr values slightly above the lower limit both in subjects with and without WMLs.1,20 Due to different vulnerabilities of cortical and subcortical resistance arterioles, exclusion of patients with cortical gray matter lesions also benefits our results.28 An important limitation of our study is the small sample size, which result in a rather low power to detect differences between subjects with and without WML. Insignificant comparisons may be due to type 2 error. Therefore, our study has the character of a pilot study. Furthermore, groups that were classified on the basis of the presence of WMLs are not well balanced, which is a further limitation. However, the number of participants was limited because of the high homogeneity of participants concerning age, gender, and the presence of hypertension. This was the basis for the lack of normotensive healthy controls in our study population. Also, to avoid a possible influence of gender on CVR, we limited our study to males. In previous studies, increased vasodilatory responses to hypercapnia in women compared with men, as well as the confounding effects of estrogen concentration on cerebrovascular resistance have been described.29–31 The question whether differences in VMRr exist between normotensive and hypertensive subjects with WMLs, and also between normotensive individuals with and without WMLs, should be addressed in future studies. Similarly, the effect of statin treatment should be explored in larger studies because previous reports described an association between statin treatment and VMRr.32,33 In our study, differences in VMRr between subjects with and without WML were not confounded by statin treatment.

Based on our results, we conclude that WMLs are a sign of focal angiopathy; however, the underlying mechanism is pathophysiologically more extensive and involves the whole vascular bed, as is demonstrated by a lower VMRr in the MCA territory. The mild extent of WML in our study population indicates that even mildly advanced clinically asymptomatic brain lesions on MRI may reflect some functional dysregulation of the cerebral vasculature in patients with arterial hypertension.

APPENDIX

Members of the SOPKARD Study Group are as follows: Grzegorz M. Kożera, MD, PhD1; Mirosława Dubaniewicz, MD, PhD2; Milena Mielczarek, MD3; Aleksandra Madej-Dmochowska, MD3; Kamil Chwojnicki, MD, PhD1; Katarzyna Kunicka, MD, PhD1; Ewa Świeblewska, MD, PhD4; Dariusz Gańcecki, MD, PhD1; Agata Ignaśewska-Wyrzykowska, MD, PhD1; Piotr Bandoz, MD, PhD1; Łukasz Matwiejczyk, MD, PhD4; Maciej Bogowicz, MD, PhD3; Marcin Rutkowski, MD, PhD3; Ewa Zdybel, MD, PhD3; Marlena Wojciechowicz, MD, PhD4; Leszek Bieniaszewski, MD, PhD4; Michal Studniarek, MD, PhD2; Tomasz Zdrojeński, MD, PhD3; Walenty M. Nyka, MD, PhD4; Barbara Krupa-Wojciechowska, MD, PhD3; Bogdan Wyrzykowski, MD, PhD4.

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Vasomotor Reactivity and White Matter Lesions


