Blood Pressure Components and Changes in Relation to White Matter Lesions
A 32-Year Prospective Population Study

Xinxin Guo, Leonardo Pantoni, Michela Simoni, Calle Bengtsson, Cecilia Björkelund, Lauren Lissner, Deborah Gustafson, Ingmar Skoog

Abstract—This study aimed to examine the long-term effect of high blood pressure (systolic blood pressure, diastolic blood pressure, pulse pressure, and mean arterial pressure) on white matter lesions and to study changes in different blood pressure components in relation to white matter lesions. A representative population of women was examined in 1968 and re-examined in 1974, 1980, 1992, and 2000. The presence and severity of white matter lesions on computed tomography were rated by a visual rating scale in 1992 and 2000 in 539 women. Systolic and diastolic blood pressures were measured at all of the examinations. We found that presence and severity of white matter lesions in 1992/2000 were associated with higher diastolic blood pressure and mean arterial pressure at each examination but not with systolic blood pressure and pulse pressure. Odds ratios (95% CIs) for the presence of white matter lesions per 10-mm Hg increase in diastolic pressure were 1.4 (1.0 to 1.9) in 1968, 1.3 (1.0 to 1.8) in 1974, 1.4 (1.1 to 1.9) in 1980, and 1.3 (1.0 to 1.6) in 1992 after adjustment for confounders. The presence of white matter lesions was also associated with a 24-year increase in diastolic pressure (>10 mm Hg), systolic pressure (>40 mm Hg), pulse pressure (>24 mm Hg), and mean arterial pressure (>6 mm Hg; odds ratios [95% CIs]: 2.6 [1.3 to 5.1] for diastolic pressure; 2.0 [1.2 to 3.4] for systolic pressure; 1.8 [1.1 to 2.7] for pulse pressure; and 2.2 [1.4 to 3.4] for mean arterial pressure). Our findings suggest that lowering high diastolic blood pressure and preventing large increases in systolic and diastolic blood pressures may have a protective effect on white matter lesions. (Hypertension. 2009;54:57-62.)

Key Words: blood pressure □ white matter lesions □ longitudinal study

Cerebral white matter lesions (WMLs) are common findings on computed tomography (CT) and MRI in the elderly.1,2 Individuals with WMLs are at increased risk for dementia,1,3 depression,4 stroke,5,6 and gait disorders.7 On histopathology, WMLs on CT represent ischemic demyelination with arteriosclerosis, hyalinosis, and narrowing of the lumen of the small penetrating arteries in the white matter.8 Cerebral ischemia and microangiopathy are suggested as the main causes of WMLs,9 and hypertension is a widely reported risk factor for these lesions.10 Higher blood pressure has been associated with an increased risk of WMLs in cross-sectional studies11,12 and in 1 short-term longitudinal study.13 However, long-term longitudinal studies on blood pressure and WMLs are few. Two such studies, 1 with 20-year follow-up in a general population14 and 1 with 25-year follow-up in a male population,15 reported an association between higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) and WMLs on MRI. An increase and decrease in DBP, as well as an increase in SBP, have also been related to higher risks of WMLs on MRI.14,16 Other than SBP and DBP, blood pressure is also characterized by its steady and pulsatile components. The mean arterial pressure (MAP) is a steady component reflecting cardiac output and vascular resistance, as well as elasticity averaged over time17,18; and pulse pressure (PP) is a pulsatile component mainly reflecting large artery stiffness and wave reflections.18 Earlier epidemiological studies have reported that PP and MAP are predictors of cardiovascular disease and stroke.17,19,20 However, it is not known how these components affect the risk of WMLs related to cerebral small-vessel diseases. Different blood pressure components may have different effects on large vessels and small vessels. Four previous prospective studies reported that higher baseline DBP, more than SBP, predicted WML progression in 2 to 5 years.21–24 The present study aimed to examine the effects of SBP, DBP, PP, and MAP on WMLs in a population-based sample.
of women with repeated blood pressure measurements during 24 years of follow-up from middle to late life.

Methods

Participants

This study is part of the Prospective Population Study of Women in Gothenburg,25–27 which was initiated in 1968–1969 with an examination of 1462 women (participation rate: 90%) born in 1908, 1914, 1918, 1922, and 1930. The population was sampled from the Swedish Population Register and was representative of women in Gothenburg at the ages studied. The women were re-examined in 1974–1975, 1980–1981, 1992–1993, and 2000–2001, giving participation rates among survivors of 91%, 83%, 70%, and 71%, respectively.

CT examinations of the brain were performed in 1992–1993 and 2000–2001. In 1992–1993, only women born in 1908, 1914, 1918, and 1922 (n=584) were invited for a brain CT scan, and 280 accepted. In 2000–2001, all of the participating women born in 1908, 1914, 1918, 1922, and 1930 (n=678) were invited for a brain CT scan and 379 accepted. Altogether, 904 women were invited for a brain CT scan in 1992 and/or 2000, and 539 (60%) participated. CT participants were younger and had a lower prevalence of hypertension (in 1968, 1974, and 1980), lower use of antihypertensive medication (in 1968, 1974, and 1980), less use of antihypertensive medication (in 1968, 1974, and 1980), less use of antihypertensive medication (in 1968, 1974, and 1980), less use of antihypertensive medication (in 1968, 1974, and 1980), and 24-year change of blood pressure. The association was tested by the ethics committee of the University of Gothenburg. All of the participants gave informed consent to participate in accordance with the provisions of the Helsinki Declaration.

Assessment of Blood Pressure and Potential Confounders

At each examination, participants underwent a physical examination performed by a physician and were also surveyed regarding a variety of background factors, eg, smoking habits, physical activity, medication use, and medical history. Blood pressure was measured with a mercury manometer in the seated position after a 5-minute rest. Blood pressure was measured to the nearest 2 mm Hg.28 PP was calculated as SBP minus DBP. MAP was calculated as 2/3 DBP + 1/3 SBP. We also calculated 24-year average blood pressure (average blood pressure in 1968, 1974, 1980, and 1992) and changes of blood pressure from 1968 to 1992. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg and/or taking antihypertensive medication at each examination.

Body height was measured to the nearest centimeter and weight to the nearest kilogram. Body mass index (BMI) was calculated in kilograms per meter squared. Blood samples were taken after an overnight fast, and serum cholesterol concentrations were measured. Regarding smoking, subjects were classified as never smokers, ex-smokers (who ceased smoking ≥1 year before examination), or current smokers. History of myocardial infarction was based on medical charts and death certificates. Diabetes mellitus was defined as a diagnosis by a doctor, being on antidiabetes therapy (insulin and/or tablets), having 2 fasting venous or capillary whole blood glucose values ≥7.0 mmol/L, or according to death certificates.

Brain CT Scans

All of the CT scans were performed without contrast enhancement. In 1992, CT scans (10-mm sections on a Philips Tomoscan 310 or a General Electric 8800) were rated by 2 experienced radiologists; and in 2000, CT scans (8-mm sections on a Picker 6000) were rated by a radiologist who was trained by one of the radiologists who examined the CT scans in 1992. All of the CT examiners were blind to the participants’ clinical characteristics. WMLs were defined as low-density areas in the periventricular and subcortical white matter. Decreased density was rated as mild, moderate, or severe, in relation to the attenuation of normal white matter. The same rating scale was used in 1992 and 2000. Interobserver agreement for rating the presence of WMLs between the 2 radiologists in 1992 was 84% (k = 0.75; P < 0.001),1 and between the radiologist in 1992 and the neurologist in 2000 it was 65% (k = 0.30; P < 0.001).

Statistical Methods

Logistic regression models were used to test the presence of WMLs in relation to DBP, SBP, PP, MAP, 24-year average blood pressure, and 24-year change of blood pressure. Ordinal regression models were used to test the severity of WMLs (no, mild, and moderate/severe WMLs) in relation to DBP, SBP, PP, MAP, 24-year average blood pressure, and 24-year change of blood pressure. The associations are presented as odds ratios (ORs) and 95% CIs, with adjustment for concurrent potential confounders (collected in the same examination as the blood pressure measurement), ie, age, CT examination year, smoking, BMI, serum cholesterol, myocardial infarction, and diabetes mellitus. These analyses were based on 539 CT scans, ie, all of the CT data in 2000 (n = 579) and CT data in 1992 for women who were not examined in 2000 (n = 160).

Changes in SBP, DBP, PP, and MAP from 1968 to 1992 were categorized into groups. The reference group of blood pressure

| Table 1. Age and Number of Participants With Brain CT and Blood Pressure Measurement by Birth Cohort |
|----------------|----------------|----------------|----------------|----------------|----------------|
| Birth Year | Blood Pressure Examination | Participants in 1992 | Brain CT | Participants in 2000 |
| -------- | ----------------- | ---------------- | ----------------- | ------------------ | ------------------ |
| 1908 | 60 (8/8) | 84 (8/8) | 84 (8/8) | 84 (6) | 92 (2) |
| 1914 | 54 (41/41) | 78 (41/41) | 78 (33) | 86 (19) | 41 |
| 1918 | 50 (142/142) | 74 (129/142) | 74 (108) | 82 (80) | 142 |
| 1922 | 46 (174/175) | 70 (169/175) | 70 (133) | 78 (105) | 175 |
| 1930 | 35 (163/173) | 62 (163/173) | 70 (173) | 173 | \n| Total | 528/539 | 518/539 | 510/539 | 510/539 | 379 | 539 |

nbp indicates the number of women with blood pressure measurement; nct, the number of women with brain CT in 1992 and/or 2000.
changes was defined as a 50% central range of blood pressure change (25th percentile to 75th percentile) in a subgroup of women without hypertension at any examinations in 1968, 1974, 1980, and 1992 (n=92). Thus, the reference groups were as follows: decrease 0 to 10 mm Hg for DBP change; increase 1 to 20 mm Hg for SBP change; increase 7 to 24 mm Hg for PP change; and decrease 6 mm Hg to 10 mm Hg for DBP change; increase 1 to 20 mm Hg for SBP change; increase 1 to 20 mm Hg for PP change; and decrease 6 mm Hg to 10 mm Hg for MAP change.

The relationships between blood pressure and WML progression (without WMLs or with mild WMLs at both examinations versus incidence plus worsening of WMLs from 1992 to 2000) were tested by logistic regression models in women having CT scan at both examinations. Age was adjusted as a confounder.


The presence of WMLs in 1992/2000 was associated with higher DBP (1968, 1980, and 1992), higher MAP (1992), and higher 24-year average DBP and MAP in multivariate-adjusted models (Table 3). The severity of WMLs in 1992/2000 was also associated with higher DBP (1968, 1980, and 1992), higher MAP (1968, 1974, and 1992), and higher 24-year average DBP and MAP (data not shown). The presence of WMLs was not related to SBP and PP at each examination or 24-year average SBP and PP.

A total of 499 women had blood pressure readings in both 1968 and 1992. Table 4 shows WMLs in relation to blood pressure changes by categories. The presence of WMLs was associated with an increase in DBP (>10 mm Hg), SBP (>40 mm Hg), PP (>24 mm Hg), and MAP (>6 mm Hg) after adjustment for multiple confounders. A decrease in MAP >6 mm Hg was associated with higher odds of WMLs after adjustment for age. However, this association disappeared after further adjustment for baseline MAP in 1968.

The associations between different blood pressure components and WMLs were further studied after excluding women with antihypertensive treatment. The magnitudes of associations between blood pressure at each examination and WMLs, as well as between changes of blood pressure and WMLs, were not changed.

The progression of WMLs from 1992 to 2000 in relation to blood pressure was studied in women having a CT scan at both examinations (n=120). Twelve women were excluded, including 3 with regressed WMLs and 9 with moderate/severe WMLs at both examinations, leaving 108 for analyses. Altogether, 27 women developed WMLs over 8 years and 16 women had worsening of WMLs from mild to moderate/severe form. Compared with women with stable WMLs (without WMLs or with mild WMLs at both examinations), women with incidence/worsening of WMLs had higher SBP, DBP, and MAP in 1992 but not in 1968, 1974, or 1980.

Age-adjusted ORs (95% CIs) were 1.23 (1.03 to 1.47), 1.44 (1.03 to 2.07), and 1.44 (1.06 to 1.96) per 10-mm Hg increase in SBP, DBP, and MAP in 1992, respectively. WML progression was not associated with baseline WML severity in 1992 or with antihypertensive medication in 1992.

### Discussion

We found that higher middle- and late-life DBP and MAP, but not SBP and PP, were associated with increased frequency and severity of WMLs on CT in a population-based sample of women followed for 32 years. Increases in DBP, SBP, PP, and MAP during follow-up were also related to the presence of WMLs. In a small sample of women examined with CT in both 1992 and 2000, higher SBP, DBP, and MAP in 1992 were associated with WML progression over 8 years.

Four prospective studies found that higher baseline DBP, better than SBP, predicted WML progression on MRI in 2 to 5 years.21–24 On the basis of a less sensitive imaging tool (CT), we also found a differential effect of SBP and DBP on WML occurrence. It should also be noted that this differential effect was consistent across all 4 of the examinations from 1968 to 1992 in the present study. However, our findings were in contrast to some previous studies reporting that both DBP and SBP were related to WMLs.7,10,11 The present study did not include whether SBP or DBP was more important in relation to WMLs. The discrepancies between our study and these previous studies may be because of

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>OR1 (95% CI)</th>
<th>OR2 (95% CI)</th>
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<tbody>
<tr>
<td>DBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1968</td>
<td>1.26 (1.13 to 1.55)</td>
<td>1.39 (1.02 to 1.89)</td>
</tr>
<tr>
<td>1974</td>
<td>1.28 (1.04 to 1.57)</td>
<td>1.29 (0.95 to 1.75)</td>
</tr>
<tr>
<td>1980</td>
<td>1.31 (1.09 to 1.59)</td>
<td>1.43 (1.08 to 1.89)</td>
</tr>
<tr>
<td>1992</td>
<td>1.24 (1.05 to 1.45)</td>
<td>1.27 (1.04 to 1.55)</td>
</tr>
<tr>
<td>Average 1968–1992</td>
<td>1.55 (1.20 to 2.01)</td>
<td>1.65 (1.12 to 2.43)</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1968</td>
<td>1.07 (0.96 to 1.19)</td>
<td>0.95 (0.80 to 1.11)</td>
</tr>
<tr>
<td>1974</td>
<td>1.08 (0.98 to 1.21)</td>
<td>0.97 (0.83 to 1.14)</td>
</tr>
<tr>
<td>1980</td>
<td>1.07 (0.98 to 1.16)</td>
<td>0.92 (0.81 to 1.05)</td>
</tr>
<tr>
<td>1992</td>
<td>1.11 (1.03 to 1.20)</td>
<td>1.02 (0.92 to 1.14)</td>
</tr>
<tr>
<td>Average 1968–1992</td>
<td>1.17 (1.04 to 1.33)</td>
<td>1.01 (0.84 to 1.21)</td>
</tr>
<tr>
<td>PP</td>
<td></td>
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<tr>
<td>1968</td>
<td>0.99 (0.86 to 1.15)</td>
<td>0.99 (0.84 to 1.15)</td>
</tr>
<tr>
<td>1974</td>
<td>1.03 (0.89 to 1.19)</td>
<td>1.00 (0.86 to 1.17)</td>
</tr>
<tr>
<td>1980</td>
<td>1.01 (0.90 to 1.13)</td>
<td>0.95 (0.84 to 1.08)</td>
</tr>
<tr>
<td>1992</td>
<td>1.07 (0.97 to 1.18)</td>
<td>1.03 (0.93 to 1.15)</td>
</tr>
<tr>
<td>Average 1968–1992</td>
<td>1.09 (0.93 to 1.29)</td>
<td>1.10 (0.93 to 1.31)</td>
</tr>
<tr>
<td>MAP</td>
<td></td>
<td></td>
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<tr>
<td>1968</td>
<td>1.17 (0.99 to 1.39)</td>
<td>1.19 (0.99 to 1.44)</td>
</tr>
<tr>
<td>1974</td>
<td>1.20 (1.01 to 1.42)</td>
<td>1.17 (0.97 to 1.41)</td>
</tr>
<tr>
<td>1980</td>
<td>1.19 (1.02 to 1.38)</td>
<td>1.13 (0.96 to 1.35)</td>
</tr>
<tr>
<td>1992</td>
<td>1.21 (1.06 to 1.38)</td>
<td>1.19 (1.02 to 1.38)</td>
</tr>
<tr>
<td>Average 1968–1992</td>
<td>1.38 (1.13 to 1.69)</td>
<td>1.46 (1.17 to 1.82)</td>
</tr>
</tbody>
</table>

OR1 was adjusted for age and CT examination year. OR2 (1968, 1974, 1980, and 1992) was adjusted for age, CT examination year, smoking, BMI, cholesterol, myocardial infarct, diabetes mellitus, antihypertensive medication, and blood pressure (OR2 DBP adjusted by SBP, and OR2 SBP adjusted by DBP) at each examination. OR2 (average 1968 to 1992) was adjusted for age, CT examination year, smoking, BMI, cholesterol, myocardial infarct, diabetes mellitus, and antihypertensive medication in 1968. OR1 and OR2 were calculated per 10-mm Hg increase of blood pressure.

differences in study design, study populations, neuroimaging methods, and length of follow-up.

It has been suggested that high DBP is mainly an indicator of peripheral resistance, whereas high SBP is mainly an indicator of large artery stiffness.30,31 The periventricular white matter harbors an arterial border zone and receives most of its blood supply from small perforating arteries and arterioles with few collaterals.8,10 It is, thus, biologically plausible that WMLs are more related to DBP than to SBP. The hypothesis that high peripheral resistance may increase the occurrence of WMLs also has been supported by the finding that WMLs were more related to higher MAP than to PP, because higher MAP more greatly reflects the resistance of the smaller arteries and higher PP more greatly reflects large artery stiffness.18

Increases in DBP, SBP, MAP, and PP during 24-year follow-up were associated with increased risk of WMLs, which was independent of baseline blood pressure and other potential confounders. To our knowledge, no study has examined the association between changes in MAP and PP in relation to WMLs, and only a few studies have examined the changes in DBP and SBP in relation to WMLs.14,16 Our study findings were in line with earlier studies that found that increases in DBP and SBP were associated with higher risk of WMLs on MRI.14,16

The strengths of this study include the long follow-up period and repeated measurements of middle- and late-life blood pressures during 24 years. Compared with cross-sectional and short-term longitudinal studies, long-term prospective studies are more valid to study the relationship between blood pressure and age-related brain changes, because blood pressure in midlife is presumably less affected by brain lesions than in later life. However, some methodological issues need to be mentioned. First, attrition because of mortality is a problem in long-term prospective studies. Compared with nonparticipants, participants in the CT examination in 1992 and 2000 were younger and had lower SBP and DBP in 1968, 1974, 1980, and 1992. Second, we combined CT data in 1992 and 2000 in the analyses. Although this led to different lengths of follow-up for different participants, the results were still consistent by year of blood pressure measurements, and separate analyses of blood pressure in relation to WMLs in 1992 and 2000 (data not shown) gave similar results as the combined analyses. In addition, the CT examination year was adjusted as a covariate in all of the analyses. Third, visual rating of WMLs on CT is a rather crude method. Interobserver agreement for the rating of WML presence was 84% (κ = 0.75) between the 2 radiologists in 1992 and 65% (κ = 0.30) between the radiologist in 1992 and the neurologist in 2000. Interobserver agreement was “good” between the 2 radiologists and “fairly good” between the radiologist and the neurologist, according to an established criteria.32 Different CT evaluators did not influence the results substantially, because the association between blood pressure and WMLs was similar in 1992 and 2000 (data not shown). Fourth, CT scans are less sensitive than MRI in detecting WMLs. However, it is important to show this association by CT, because CT is still the most widely used neuroimaging worldwide. WMLs on CT might show this association by CT, because CT is still the most widely used neuroimaging worldwide. WMLs on CT might have more clinical consequences than those on MRI, because the prevalence of WMLs on MRI is very high, and the importance of WMLs might be underestimated by MRI. It has been reported that WMLs on CT better predict later development of cerebrovascular disorders than WMLs noted on MRI, supporting the view that CT may be more specific and informative in detecting brain lesions than in later life. However, some methodological issues need to be mentioned. First, attrition because of mortality is a problem in long-term prospective studies. Compared with nonparticipants, participants in the CT examination in 1992 and 2000 were younger and had lower SBP and DBP in 1968, 1974, 1980, and 1992. Second, we combined CT data in 1992 and 2000 in the analyses. Although this led to different lengths of follow-up for different participants, the results were still consistent by year of blood pressure measurements, and separate analyses of blood pressure in relation to WMLs in 1992 and 2000 (data not shown) gave similar results as the combined analyses. In addition, the CT examination year was adjusted as a covariate in all of the analyses. Third, visual rating of WMLs on CT is a rather crude method. Interobserver agreement for the rating of WML presence was 84% (κ = 0.75) between the 2 radiologists in 1992 and 65% (κ = 0.30) between the radiologist in 1992 and the neurologist in 2000. Interobserver agreement was “good” between the 2 radiologists and “fairly good” between the radiologist and the neurologist, according to an established criteria.32 Different CT evaluators did not influence the results substantially, because the association between blood pressure and WMLs was similar in 1992 and 2000 (data not shown). Fourth, CT scans are less sensitive than MRI in detecting WMLs. However, it is important to show this association by CT, because CT is still the most widely used neuroimaging worldwide. WMLs on CT might have more clinical consequences than those on MRI, because the prevalence of WMLs on MRI is very high, and the importance of WMLs might be underestimated by MRI. It has been reported that WMLs on CT better predict later development of cerebrovascular disorders than WMLs noted on MRI, supporting the view that CT may be more specific and that only severe WMLs are of clinical relevance.33 Finally, CT scans were not conducted in 1968, 1974, and 1980. Thus, we cannot exclude the possibility that some women might have had these brain changes already in midlife. However, most of the women were healthy and young at the baseline examinations, and, thus, the prevalences of WMLs were probably low, especially the severe form.

Perspectives

We found that women with high DBP and MAP in middle and late life, as well as women having increases in DBP, SBP, MAP, and PP during follow-up more frequently presented WMLs in later life. Our findings suggest that increased peripheral resistance may increase the occurrence of WMLs.
Lowering high DBP and preventing large increases in SBP and DBP may have a protective effect on cerebral WMLs.

Sources of Funding

This study has been supported by grants from the Swedish Medical Research Council (27x-4578), the Alzheimer’s Association Zenith Award (ZEN-01-3151), Stiftelsen Fo¨r Gamla Tjan¨arinor, Handlanden Hjalmar Svenssons Forskningsfond, and S¨oderstro¨m-Ko¨nigska Sjukhemmet.

Disclosures

None.

References


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Hypertension. 2009;54:57-62; originally published online June 1, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.129700

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