Systemic Blood Pressure Profile in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

Alessandra Rufa, MD; Maria Teresa Dotti, MD; Massimo Franchi, MD; Maria Laura Stromillo, MD; Gabriele Cevenini, PhD; Silvia Bianchi, PhD; Nicola De Stefano, MD; Antonio Federico, MD

Background and Purpose—Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic form of subcortical ischemic vascular dementia (SIVD). The most common vascular risk factors are unremarkable in CADASIL; however, studies on systemic blood pressure (BP) changes over time are substantially lacking. Because BP instability is a relevant risk factor for developing or worsening white matter changes in sporadic SIVD, we aimed to study the BP profile of CADASIL to investigate its relationship with cognitive decline and white matter injury.

Methods—Twenty-four–hour ambulatory BP monitoring was performed in a group of 14 CADASIL patients (12 males and 2 females) and in a group of 15 healthy age-matched control subjects. The following BP variables were compared between the 2 groups: mean daytime and nighttime systolic, diastolic, and mean arterial BP (SABPday, DABPday, and MABPday and SABPnight, DABPnight, and MABPnight) and nocturnal percentage decline in arterial BP (%MABP reduction). Cognitive performances were tested by mini mental status examination (MMSE), and brain MRI was performed to extrapolate the T2-weighted lesion volume (LV) in each CADASIL patient. The 24-hour arterial BP variables were compared between CADASIL and controls. In addition, for CADASIL patients only, MMSE, LV, and age were compared with each pressure variable.

Results—Patients with CADASIL showed a significant reduction ($P < 0.05$) of SABPday, DABPday, MABPday and %MABP decline with respect to controls. In addition, MMSE of CADASIL subjects correlated significantly ($P < 0.0001$) with daytime MABP.

Conclusions—The low systemic BP profile observed in CADASIL patients was specifically attributable to reduced diurnal BP values. This may further affect cerebral hemodynamics and increase the risk of cognitive impairment in these patients. The pathogenesis of abnormal BP profile in CADASIL remains to be clarified. It is likely that central and peripheral mechanisms controlling BP variations are involved. (Stroke. 2005;36:2554-2558.)

Key Words: blood pressure ■ CADASIL ■ dementia ■ magnetic resonance imaging

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a generalized small- and medium-sized arteriopathy attributable to mutations in the Notch3 gene,¹ which causes repeated strokes, MRI evidence of diffuse white matter (WM) changes, and progressive cognitive impairment.² Although the nature of Notch3 mutations is highly stereotyped,³ the phenotypic expression of the disease is extremely variable,³ suggesting a possible modulating role of other genetic or acquired factors, including cardiovascular risk factors.⁴,⁵ Vascular smooth muscle cells are thought to be targeted by the disease.⁶ Their degeneration presumably leads to loss of systemic arteriolar wall tone and failure of cerebral autoregulation with chronic hypoperfusion or abrupt lack of perfusion.⁷ Unlike in other forms of sporadic subcortical ischemic vascular dementia (SIVD), arteriolar occlusions were rarely observed in autopsied cases.⁸ However, the exact mechanism of how the alterations of the deep small penetrating arteries cause WM changes and lacunar infarcts characteristic of CADASIL are still debated.⁹,¹⁰ Cerebral WM abnormalities similar to those observed in CADASIL patients, are frequently seen on MRI of elderly individuals, particularly in those with vascular risk factors and with cognitive impairment.¹¹ Blood pressure (BP) instability is a serious risk factor for developing or worsening WM changes in sporadic SIVD because prolonged hypertensive or conversely hypotensive...
state is associated with increased risk of cerebral WM changes and dementia.12–14

Unlike SIVD, the common vascular risk factors are unremarkable in CADASIL; nevertheless, studies on systemic BP changes over time are lacking. The aim of the present study was to determine the BP profile in 14 CADASIL patients and to investigate its relationship with cognitive decline and MRI evidence of WM changes.

Materials and Methods

Subjects

Fourteen CADASIL patients (12 males and 2 females; mean age 48.1; range 25 to 70) from 10 families were recruited. None of them experienced acute vascular events or migraine with aura in the 3 months preceding and during the study. No cardiac disease was reported in their clinical history. The following clinical features were recorded: first symptom and age of onset, global cognitive performance evaluated by mini mental status examination (MMSE;15 dementia defined as MMSE <23), and functional ability at the time of investigation by Rankin scale.

CADASIL patients underwent complete general and laboratory assessment, including vascular risk factors (smoking history, cholesterol, triglycerides, glucose, homocysteine, complete blood cell count, electrocardiography, echocardiography, and carotid Doppler sonography). Three patients were taking aspirin at the time of enrollment. All patients underwent neuropsychological evaluation and conventional MRI examination.

Control subjects were white, nonsmoking, healthy age-matched volunteers (5 females and 10 males; mean age 46.2; range 25 to 73). Exclusion criteria for controls included obesity, history of cerebral or heart disease, and personal or family history of risk factors for vascular disease. All subjects gave informed consent, and the study was approved by the regional ethics committee.

BP Profile Assessment

Basal BP was measured with a mercury sphygmomanometer either in the right or left arm in the seated position after 5 minutes of rest. Twenty-four-hour ambulatory BP monitoring was performed in the right arm in 2 sessions separated by a 3-month interval in each subject using Novacor Dynasis Integra equipment to assess circadian pattern, and the values of the 2 measurements were averaged. The instrument is a noninvasive portable automatic ambulatory BP recorder operating in each standard auscultatory and oscillometric mode. Recordings were performed in auscultatory mode based on detection of appearance and disappearance of Korotkoff sounds. Systolic and diastolic arterial BP (SABP and DABP, respectively) and heart rate were averaged over successive 20-minute intervals through the day (from 7 AM to 12 PM) and 30-minute intervals at night (from 12 PM to 7 AM). Mean arterial BP (MABP) was computed automatically by the equipment; overall diurnal and nocturnal values and percentage nocturnal dipping of MABP (%MABP reduction) [(BPday − BPnight)/BPday] × 100], were also calculated by the instrument. Only effective records (≥50% of probes and measurements per hour) were examined for each patient. On the basis of nocturnal MABP dipping, patients were classified as extreme dippers (MABP reduction ≥20%), dippers (≥10% but <20%), nondippers (<10% but ≥0%), and inverted dippers (<0%). Hypertension was defined as persistent baseline SABP ≥160 mm Hg or DABP ≥95 mm Hg or current treatment with antihypertensive drugs. Conversely, hypotension was considered SABP ≤110 mm Hg and DABP ≤70 mm Hg (subcommittee of World Health Organization/International Society of Hypertension Mild Hypertension Liaison Committee 1993).

MRI Examination and Analysis

All patients were examined using the same magnetic resonance protocol, which included combined proton MRI of the brain obtained in a single session of 50 minutes for each examination using a Philips Gyroscan operating at 1.5 T (Philips Medical Systems). A transverse dual-echo, turbo spin-echo sequence (repetition time/echo time 1/echo time 2=2075/30/90 ms, 256×256 matrix, 1 signal average, 250 mm field of view) yielding proton density (PD) and T2-weighted (T2W) images with 50 contiguous 3-mm slices was acquired parallel to the line connecting the anterior and posterior commissures.

Classification of T2W lesion volume (LV) was performed in each patient by a single observer (M.L.S.) using a segmentation technique based on user-supervised local thresholding unaware of subject identity. Lesion borders were determined primarily on PD-weighted images, but information from T2W and T1W images was also considered because the software (Jim 3.0; Xinapse System) offered the possibility of switching between PD, T2W, and T1W images, providing the operator with convenient access to the information in both data sets while defining lesions and facilitating discrimination of cerebrospinal fluid and periventricular plaque. Total brain LV was calculated by multiplying lesion area by slice thickness and was reproducible to ~3% in serial measurements.

Statistical Analysis

All the pressure variables (SABPday, DABPday, MABPday, SABPnight, DABPnight, and MABPnight) and nocturnal percentage decline in arterial BP (% MABP reduction) were compared between CADASIL and controls using Student t test for equal or unequal group variance. The Mann–Whitney U test was also applied to reinforce the t test statistical results. Equality of group variances was first tested by Levene statistics.

For CADASIL patients only, paired association between MMSE, LV, and all pressure variables was evaluated by the Pearson correlation coefficient r. Correlation was also tested between MMSE and LV.

A probability error P<0.05, corresponding to a significance level >95%, was chosen for the significance of all statistical computing. Statistical analysis was performed with the SPSS computer package.

Results

Clinical Characteristics and Risk Factors (Table 1)

The age at onset of the first symptom ranged from 17 to 66 years. Only 1 patient was currently asymptomatic (25 years of age). Symptoms at onset were: acute ischemic cerebrovascular episodes in 9 subjects (presenting as ocular manifestations in 4 of them), migraine with or without aura in 2, and depression in 2. The following cardiovascular risk factors were found: hyperhomocysteinemia in 5 of 14, hypercholesterolemia in 3 of 14, current smokers 2 of 14, and ex-smokers 2 of 14. No diabetes, hypertension, significant heart disease, or carotid stenosis was found. At recruitment, stroke/TIA had occurred in 11 of 14 patients, migraine in 2 of 14, and dementia (MMSE corrected for age, socioeconomic, and educational variables <23) in 8 of 14. Only 2 patients were moderately disabled (Rankin score 3), whereas the majority of patients mildly disabled (11 patients; Rankin score 1 to 2), or normal (1 patient; Rankin score 0).

BP Profile

No significant differences were observed on basal conditions between left and right brachial BP measurements.

Among all the measured parameters, a statistically significant difference (P<0.05) was observed between CADASIL and controls for: MABPday, SABPday, DABPday, and %MABP reduction. Nocturnal BP variables did not show any statistical differences (Table 2).

Based on percentage nocturnal fall in MABP, 9 CADASIL patients were nondippers (%MABP decline was respectively: 4% in 2, 5% in 2, 6% in 3, and 8% in 2), 3 dippers...
(respectively 10%, 12%, and 14%), 1 extreme dipper (21%), and 1 was an inverted dipper (21%). Among normal subjects: 11 were dippers (%MABP reduction was respectively: 19% in 1, 18% in 3, 17% in 3, 16% in 2, and 15% in 2); 3 extreme dippers (20%, 22%, and 27%, respectively), and 1 nondipper (10%). Comparison of mean, SABPday, DABPday, and MABPday revealed a significantly lower daily BP profile (SABPday 111.7 mm Hg range 102 to 118; DABPday 74.4 mm Hg range 68 to 76; MABPday 86.5 mm Hg range 80 to 97) in CADASIL patients than normal subjects (SABPday 126.4 mm Hg range 118 to 133; DABPday 82.2 mm Hg range 76 to 86 and MABPday 96.9 mm Hg, range 91 to 103). Figure 1 shows the 24-hour differences in MABPday and percentage reduction in MABP between CADASIL and controls. Average 24-hour MABP values revealed a reduced BP variability, mostly because of lower daily MABP values in CADASIL patients than controls (Figure 2). By comparing each BP variable with global cognitive performances and magnetic resonance volume of tissue damage, a positive correlation was found between MMSE score and MABPday (r=0.834; P<0.0001). No correlations were observed between pressure variables or MMSE and T2W MRI LV.

**Discussion**

Studies on BP profile are substantially lacking in CADASIL. Here, we demonstrated for the first time a significant reduction in mean diurnal systolic and diastolic BP in CADASIL.

**TABLE 1. Phenotypic and Genetic Profile**

<table>
<thead>
<tr>
<th>Patient (sex)</th>
<th>Age/Onset</th>
<th>First Symptom</th>
<th>MMSE</th>
<th>Rankin Score</th>
<th>MRI Lesion Load cm³</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG (M)</td>
<td>60/31</td>
<td>permanent visual loss (ION)</td>
<td>24</td>
<td>3</td>
<td>63.7</td>
<td>R110C</td>
</tr>
<tr>
<td>PN (M)</td>
<td>31/17</td>
<td>transient visual loss</td>
<td>20</td>
<td>2</td>
<td>NP</td>
<td>R110C</td>
</tr>
<tr>
<td>PPG (M)</td>
<td>25/...</td>
<td>asymptomatic</td>
<td>28</td>
<td>0</td>
<td>1.46</td>
<td>R110C</td>
</tr>
<tr>
<td>FR (M)</td>
<td>42/23</td>
<td>confusion episode</td>
<td>22</td>
<td>1</td>
<td>67.03</td>
<td>C183S</td>
</tr>
<tr>
<td>DPM (F)</td>
<td>55/48</td>
<td>migraine with aura</td>
<td>19</td>
<td>1</td>
<td>63.7</td>
<td>*Fs aa 127–158 Stop codon aa 159</td>
</tr>
<tr>
<td>TG (M)</td>
<td>70/66</td>
<td>depression</td>
<td>12</td>
<td>3</td>
<td>124.28</td>
<td>R607C</td>
</tr>
<tr>
<td>TP (M)</td>
<td>47/42</td>
<td>hemiparesis</td>
<td>27</td>
<td>0</td>
<td>15.03</td>
<td>R1006C</td>
</tr>
<tr>
<td>SS (M)</td>
<td>57/48</td>
<td>depression</td>
<td>14</td>
<td></td>
<td>NP</td>
<td>R607C</td>
</tr>
<tr>
<td>TA (M)</td>
<td>47/40</td>
<td>hemiparesis</td>
<td>22</td>
<td>1</td>
<td>39.9</td>
<td>R1079C</td>
</tr>
<tr>
<td>TS (M)</td>
<td>41/38</td>
<td>migraine</td>
<td>26</td>
<td>1</td>
<td>4.6</td>
<td>R1076C</td>
</tr>
<tr>
<td>FD (M)</td>
<td>42/36</td>
<td>hemiparesis</td>
<td>19</td>
<td>2</td>
<td>121.49</td>
<td>R332C</td>
</tr>
<tr>
<td>FF (M)</td>
<td>58/56</td>
<td>double vision</td>
<td>28</td>
<td>1</td>
<td>179.55</td>
<td>R169C</td>
</tr>
<tr>
<td>GP (F)</td>
<td>64/64</td>
<td>double vision</td>
<td>27</td>
<td>1</td>
<td>71.6</td>
<td>C174Y</td>
</tr>
</tbody>
</table>

*Heterozygous deletion of 5 bp (Del 458_462TTGTG) in exon 4 of Notch3 gene. ION indicates ischemic optic neuropathy.

**TABLE 2. Statistical Comparison of Differences Between CADASIL Patients and Control Subjects**

<table>
<thead>
<tr>
<th>Pressure Variables</th>
<th>Group</th>
<th>Range of BP Values, mm Hg</th>
<th>Mean±SD</th>
<th>Student t Test, P Value</th>
<th>Mann–Whitney U Test, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%MABP reduction</td>
<td>CADASIL</td>
<td><del>21</del>+2%</td>
<td>7.9±5.6%</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>~27%~12%</td>
<td>17.6±3.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SABP&lt;sub&gt;day&lt;/sub&gt;</td>
<td>CADASIL</td>
<td>102~118</td>
<td>111.7±3.8</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>118~133</td>
<td>126.4±6.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DABP&lt;sub&gt;day&lt;/sub&gt;</td>
<td>CADASIL</td>
<td>68~76</td>
<td>74.4±2.8</td>
<td>&lt;0.001</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>76~86</td>
<td>82.2±3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MABP&lt;sub&gt;day&lt;/sub&gt;</td>
<td>CADASIL</td>
<td>80~97</td>
<td>86.5±4.8</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>91~103</td>
<td>96.9±3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SABP&lt;sub&gt;night&lt;/sub&gt;</td>
<td>CADASIL</td>
<td>87~114</td>
<td>100.8±9.1</td>
<td>0.524</td>
<td>0.414</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>90~115</td>
<td>103.0±7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DABP&lt;sub&gt;night&lt;/sub&gt;</td>
<td>CADASIL</td>
<td>59~83</td>
<td>68.5±6.8</td>
<td>0.296</td>
<td>0.300</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>58~73</td>
<td>65.6±6.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MABP&lt;sub&gt;night&lt;/sub]</td>
<td>CADASIL</td>
<td>70~91</td>
<td>79.5±7.4</td>
<td>0.726</td>
<td>0.703</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
<td>69~89</td>
<td>78.7±4.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
patients with respect to age- and sex-matched healthy controls. We also confirmed the reduced nocturnal BP decline observed previously in a few cases.16

CADASIL is an inherited form of SIVD attributable to small artery disease. As in sporadic SIVD, MRI studies of CADASIL patients have revealed a microangiopathic pattern of signal abnormalities, including diffuse WM hyperintensities in T2 signal sequences and circumscribed subcortical lesions.17 Unlike sporadic SIVD, the most common cardiovascular risk factors were unremarkable in a large sample of CADASIL patients except for smoke and hyperhomocysteinemia which, in a previous study, significantly correlated with increased risk of stroke and migraine.4 The mechanisms leading to WM hyperintensities and lacunar infarcts in CADASIL are still debated. Decreasing or loss of cerebral vasoreactivity is commonly considered the pathophysiologic key, primarily responsible for the hemodynamic changes leading to subcortical chronic hypoperfusion and ischemic lacunar lesions.18,19,20 This would make the WM more susceptible to decline in blood flow during systemic hypotension.

In this study, we found an atypical systemic BP profile with reduced 24-hour variability in BP in 14 CADASIL patients in different stages of the disease and a reduced percentage of MABP decline with respect to controls. The differences in the average of circadian MABP variation between the 2 groups were mostly attributable to MABP daily values, which were lower in CADASIL (Figure 2). In fact, no significant differences were observed during nighttime. Probably, reduced daily BP values may be contributing to a lower percentage of nocturnal MABP decline in our CADASIL patients.

The pathogenesis of abnormal BP profile in CADASIL remains to be clarified. It is likely that central and peripheral mechanisms controlling BP variations are involved. Peripheral compensatory mechanisms of BP regulation may be impaired in CADASIL. Systemic peripheral small vessels show the characteristic pathological features of the disease consisting of degeneration of vascular smooth muscle cells and accumulation of granular osmiophilic material,21,22 which may result in hemodynamic consequences on peripheral resistance arteries. In this respect, early damage of resistance artery responses to flow and pressure has been shown in a mouse model of CADASIL.22 In vivo, a selective systemic microvascular vasoconstrictor abnormality and severe weakness of the arteriolar wall were also reported.23 One interpretation might be that reduced BP variability, found in our patients with respect to controls, reflects an abnormal responsiveness of peripheral resistance arteries during daily life, when the mechanisms of BP regulation are more stressed. The difference is unremarkable during nighttime. Alternatively, the low BP profile may be attributable to functional failure of brain structures and connections controlling circadian BP variations, secondary to the extensive WM damage observed in most cases. The latter cannot be excluded by the present study. An alternative hypothesis is the involvement of peripheral and central mechanisms controlling BP variability in different stages of the disease.

The low daytime MABP significantly correlated with global cognitive impairment (MMSE) in our patients. As extensively reported in previous studies, a lower BP profile increases the risk of leukoaraiosis and dementia in elderly people.24,25 The BP profile seems to be relevant for different outcomes of patients with SIVD, tending to elevate over time in patients with a fair outcome and to decrease in those with lacunar infarcts and diffuse WM changes who developed dementia and symptomatic infarcts.26,27 We cannot draw final conclusions about the mechanism underlying the correlation between MMSE and MABP daily. Systemic BP below a critical threshold could result in cerebral hypoperfusion in CADASIL patients who already have impaired cerebral hemodynamics and impaired cerebral vasoreactivity.18 We hypothesize on this basis that dementia may be worsened by a low BP profile, not only in terms of WM changes but probably also in terms of hippocampal and
cortical damage. Recent data on SIVD\(^28\) and CADASIL patients showing the presence of cortical damage seem to support this hypothesis. In CADASIL, some evidences suggest a cortical damage: (1) cortical vessel structural abnormalities,\(^9\) (2) cortical functional impairment,\(^29\) and (3) cortical atrophy.\(^30\)

In conclusion, our results suggest that low BP profile may be part of the clinical features in patients with CADASIL and that may be a further risk factor for global cognitive deterioration. The mechanism by which abnormal BP profile modulates the clinical course of disease needs to be further investigated in longitudinal studies.

Acknowledgments

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References


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