Cerebral Hemodynamics and Malignant Hypertension

Rogier V. Immink, Bert-Jan H. van den Born, Gert A. van Montfrans, Yu-Sok Kim, Markus W. Hollmann, Johannes J. van Lieshout

Abstract—In patients with malignant hypertension, immediate blood pressure reduction is indicated to prevent further organ damage. Because cerebral autoregulatory capacity is impaired in these patients, a pharmacologically induced decline of blood pressure reduces cerebral blood flow with the danger of cerebral hypoperfusion. We compared the reduction in transcranial Doppler–determined middle cerebral artery blood velocity during blood pressure lowering with sodium nitroprusside with that of labetalol. Therefore, in 15 patients, fulfilling World Health Organization criteria for malignant hypertension, beat-to-beat mean arterial pressure, systemic vascular resistance (Modelflow), mean middle cerebral artery blood velocity, and cerebrovascular resistance index (mean blood pressure:mean middle cerebral artery blood flow velocity ratio), were monitored during treatment with sodium nitroprusside (n=8) or labetalol (n=7). The reduction in mean arterial blood pressure with sodium nitroprusside (−28±3%; mean±SEM) and labetalol (−28±4%) was comparable. With labetalol, both systemic and cerebral vascular resistance decreased proportionally (−13±10% and −17±5%), whereas with sodium nitroprusside, the decline in systemic vascular resistance was larger than that in cerebral vascular resistance (−53±4% and −7±4%). The rate of reduction in middle cerebral artery blood velocity was smaller with labetalol than with sodium nitroprusside (0.45±0.05% versus 0.78±0.04% cm·s⁻¹·%mm Hg⁻¹; P<0.05). In conclusion, sodium nitroprusside reduced systemic vascular resistance rather than cerebral vascular resistance with a larger rate of reduction in middle cerebral artery blood velocity, suggesting a preferential blood flow to the low resistance systemic vascular bed rather than the cerebral vascular bed. (Hypertension. 2008;52:236-240.)

Key Words: cardiovascular disease/stroke  ■ other hypertension  ■ Doppler ultrasound  ■ transcranial Doppler  ■ cardiovascular pharmacology

Malignant hypertension and hypertensive encephalopathy are hypertensive emergencies, characterized by a severe elevation of blood pressure (BP) and impaired cerebral autoregulation (CA).¹ CA is defined as the capacity to maintain constancy of cerebral blood flow (CBF) despite changes in mean arterial pressure (MAP). Normally CA is preserved for a range of MAP from ~60 to 150 mm Hg, respectively the lower and upper limits of CA. In patients with moderate hypertension, the autoregulation curve is shifted toward higher BP values, protecting the brain from hyperperfusion.² However, in patients with malignant hypertension, BP is supposed to surpass the upper limit of CA with loss of control of cerebral perfusion. Under those circumstances, CBF becomes a function of arterial pressure, so-called pressure dependency.³ Therefore, the initial reduction in BP is restricted to ~25% of the presenting level to avoid symptomatic hypoperfusion of the brain.⁴–⁶

Of the therapeutic agents available, sodium nitroprusside (SNP) and labetalol are commonly used for the initial parenteral treatment of malignant hypertension.⁵⁷ SNP, an arteriolar and venous vasodilator, is widely advocated as a first-line agent in the treatment of malignant hypertension.⁶,⁸,⁹ It is effective within seconds and has a short half-life, making it most suitable for an immediate and controlled reduction of BP. Despite its superior pharmacokinetics, SNP has some disadvantages, which may hamper its use. First, with SNP infusion, intracranial pressure may rise,¹⁰ although in subjects with intact CA, CBF velocity is preserved.¹¹ Second, there is a dose-dependent risk of cyanide and thiocyanide toxicity.¹² Labetalol, an α- and β-adrenergic blocker, has a slower onset of action with a maximal hypotensive effect within 5 to 15 minutes.⁴ Its long half-life of 4 to 6 hours limits the ability to promptly correct hypotension with cessation of the drug.¹³ In

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Labetalol vs SNP in Malignant Hypertension

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Treatment
With intravenous labetalol or SNP, MAP was reduced ~25% below the presenting value. The order of the open-label administration of the 2 drugs was not randomized, because the admittance rate of patients with proven malignant hypertension in the Netherlands is fairly small. The first 8 patients were treated with SNP and described in an earlier report. SNP infusion was started at 0.3 μg·kg⁻¹·min⁻¹, increased to 0.5 μg·kg⁻¹·min⁻¹ after 5 minutes and, from then on, by 0.5 μg·kg⁻¹·min⁻¹ every 5 minutes (with a maximum of 5 μg·kg⁻¹·min⁻¹). In the present study, 7 patients were treated with labetalol administered in boluses of 0.5 mg·kg⁻¹ every 8 minutes with a maximum of 200 mg. When the desired MAP reduction was achieved, a continuous infusion of 20 mg·h⁻¹ was started.

Measurements
Patients were instrumented with ECG electrodes. Intra-arterial BP was monitored through a catheter (1.1-mm ID, 20 gauge) placed in the radial artery. Heart rate was the inverse of the interbeat interval. Stroke volume (SV) was determined by a 3-element model of arterial input impedance (ModelFlow). SV was calculated from the BP waveform using the model flow method incorporating age, sex, height, and weight (BeatScope 1.0 software, BMEye). This technique tracks fast changes in SV. SV was expressed as the percentage change of the presenting value, cardiac output was heart rate times SV, and SVR was the ratio of MAP/cardiac output. The middle cerebral artery blood velocity (MCA V) was measured in the proximal segment of the right middle cerebral artery (Multidop X4). Once the optimal signal/noise ratio was obtained, the probe was secured with a headband (Mark 600, Spencer Technologies). The cerebrovascular resistance index (CVRI) was expressed as the ratio of MAP:MCA Vmean.

Data Analysis
Data were expressed as means±SEM. Changes in CBF were tracked by MCA Vmean and integrity of CA is reflected by constancy of MCA Vmean despite changes in MAP. For assessment of CA, the signals of MCA V and BP were first averaged to 30-second episodes and then were linearly related to each other. To compare CA between groups, MAP and MCA Vmean were expressed as the percentage change of pretreatment values.

Dynamic CA was determined by calculating the power spectra of pressure and velocity in the frequency domain from a 3-minute episode of beat-to-beat data of MAP and MCA Vmean before BP lowering treatment with discrete Fourier transform, after spline interpolation and resampling at 4 Hz. Results were expressed as the integrated area in the low frequency range (0.07 to 0.15 Hz). To examine the strength between low-frequency MAP and MCA Vmean coherence was used to signify that the 2 cardiovascular signals covary significantly. The squared coherence function reflects the fraction of output power (MCA Vmean) that can be linearly related to the input power (MAP). From the MAP to MCA Vmean cross-spectrum, the MCA Vmean to MAP phase lead (degrees) was obtained. A phase difference below ~50° was considered abnormal.

Statistical Analysis
Changes in systemic and cerebral hemodynamics during treatment were examined by Friedman ANOVA on ranks. Differences in CA between labetalol and SNP treatment (unpaired) and before and after treatment (paired) were examined with Wilcoxon rank sum test and Wilcoxon signed rank test, respectively. A value of P<0.05 was considered to indicate a statically significant difference.

Results
Patient characteristics, systolic and diastolic BP (Table 1), and MCA Vmean (64±6 versus 58±8 cm·s⁻¹) did not differ between SNP and labetalol. The MCA Vmean to MAP phase difference was equally affected for SNP (30±8°) and labe-
talol (26±9°) with comparable coherences (0.64±0.04 and 0.59±0.05, respectively).

Target BP was reached within 60 minutes in all of the patients. Changes in systemic and cerebral hemodynamics are given in Table 2. The reduction in MAP with SNP (28±3%) and labetalol (28±4%) was comparable. SVR and CVRi declined to the same extent (−13±10% and −17±5%) during treatment with labetalol, whereas with SNP the decrease in SVR (−53±4%) was larger than the decrease in CVRi (−7±4%; P<0.05; Figure 1). The rate of reduction in MCA Vmean with labetalol was smaller compared with SNP (0.45±0.05 versus 0.78±0.04% cm/s·mm Hg⁻¹; P<0.05; Figure 2).

### Discussion

In patients with malignant hypertension the therapeutic challenge is to reduce BP without jeopardizing the cerebral circulation against the background of impaired CA. In this study the reduction in MAP with SNP and labetalol was comparable, but the decline in MCA Vmean with labetalol versus SNP was less significant for a given reduction in BP. This could be attributed to different effects of the 2 agents on the systemic and cerebral vascular beds. With labetalol, SVR decreased proportionally to cerebral vascular resistance with a relatively small rate of reduction in MCA Vmean. In contrast, SNP reduced systemic rather than cerebral vascular resistance resulting in a preferential blood flow to the systemic vascular bed with a considerable reduction in cerebral blood velocity per unit BP. A deviation of blood flow with SNP has been reported earlier for the coronary circulation in patients with coronary artery disease where SNP treatment moved blood flow away from the ischemic myocardium to the coronary arteries.

### Malignant Hypertension and CA

CA is defined as the intrinsic capacity of cerebral vasculature to maintain constant CBF. Maintenance of cerebral perfusion during physiological challenges is secured by both fast- and slow-acting autoregulatory mechanisms. Although acute changes in BP are transmitted to the cerebral circulation, under normal conditions CBF tends to return to its baseline value within a few seconds. This short-term control is usually referred to as dynamic CA. Static CA considers the net change in CBF resulting from a manipulated change in cerebral perfusion pressure under steady-state conditions.

### Table 2. Patient Characteristics and BP on Admission

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SNP</th>
<th>Labetalol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Age, y</td>
<td>44±5</td>
<td>40±5</td>
</tr>
<tr>
<td>Gender, m:f</td>
<td>6:2</td>
<td>5:2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175±5</td>
<td>172±5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76±5</td>
<td>73±5</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>225±5</td>
<td>227±5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>137±3</td>
<td>133±4</td>
</tr>
</tbody>
</table>

Data show brachial cuff BP. Data are means±SEMs unless otherwise specified.

### Table 2. Hemodynamic Variables Before and After Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>SNP Before</th>
<th>SNP After</th>
<th>Labetalol Before</th>
<th>Labetalol After</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>155±6</td>
<td>112±6*</td>
<td>166±7</td>
<td>118±5*</td>
</tr>
<tr>
<td>HR, min⁻¹</td>
<td>87±7</td>
<td>102±6*</td>
<td>99±8</td>
<td>76±6†</td>
</tr>
<tr>
<td>CO, %</td>
<td>100</td>
<td>109±4</td>
<td>100</td>
<td>109±9</td>
</tr>
<tr>
<td>SVR, %</td>
<td>100</td>
<td>131±8*</td>
<td>100</td>
<td>86±9†</td>
</tr>
<tr>
<td>MCA Vmean, cm·s⁻¹</td>
<td>64±6</td>
<td>50±5*</td>
<td>58±8</td>
<td>49±5*</td>
</tr>
</tbody>
</table>

**SNP** indicates heart rate; **CO**, cardiac output. Data are means±SEMs unless otherwise specified.

*P<0.05 vs before treatment.
†P<0.05 vs after treatment with SNP.

**Figure 1.** Systemic and cerebral vascular resistance during blood pressure reduction. Percentage change in SVR (■), and cerebral vascular resistance (□) during a decrease in blood pressure with SNP and labetalol. Mean±SEM, *P<0.05. Note that with SNP, SVR decreases and CVRi tends to increase, whereas with labetalol both SVR and CVRi decline proportionally.

**Figure 2.** MAP-middle cerebral artery blood velocity relationship. Reduction in MCA Vmean during a decrease in MAP by SNP (●; n=8) vs labetalol (○; n=7). The rate of reduction in MCA V was smaller with labetalol than with SNP (0.45±0.05 vs 0.78±0.04% cm·s⁻¹·% mm Hg⁻¹; P<0.05; Figure 2).
to normotensive subjects, CBF remains unaltered, conforming the maintained integrity of CA.  

When BP decreases below ≈60 mm Hg in normotensive subjects, ie, below what is considered the lower limit of CA, CBF decreases proportionally with BP. The majority of patients with malignant hypertension have a history of chronic hypertension, and in those patients the lower limit of CA has been shifted in proportion toward higher pressures. For obvious reasons, the upper limit of CA has not been determined in normotensive or hypertensive humans. It was located between 120 and 150 mm Hg in normotensive baboons and between 155 and 170 mm Hg in baboons with experimental renovascular hypertension. In the present study, MAP on admission was ≈160 mm Hg and assumed to be located around, or just above, the upper limit of the CA plateau. With intact CA, during treatment more or less constancy of MCA Vmean was expected between ≈160 and ≈115 mm Hg, ie, within the CA range. Instead, the observation that, either with SNP or labetalol, MCA Vmean decreased linearly with MAP suggests serious impairment of static CA.

Considerations

Critical for the interpretation of the data is to what extent MCA Vmean reflects volume flow. The MCA Vmean was calculated from the frequency distribution of the Doppler shifts and was assumed to represent maximal flow velocity in the center of the vessel. Changes in MCA Vmean, however, reflect changes in flow, only as long as the diameter of the MCA remains constant during SNP or labetalol treatment. Direct observations made during craniotomy have revealed that SNP does not affect the vessel diameter of the MCA. Also, constancy of MCA diameter was demonstrated for a range of pressures. Therefore, we considered that, in this study, changes in MCA Vmean were proportional to those in flow.

Improvement of symptoms of hypertensive encephalopathy or visual disturbances takes place after several days to weeks. The study period was too short to notice such improvement, although some patients reported a relief of headache within the study period. Another potential limitation was that the order of the open-label administration of the 2 drugs was not randomized. Our earlier observations on MCA Vmean during parenteral BP lowering were with SNP. We now report the findings in a group of similar patients with malignant hypertension using labetalol intravenously and compared cerebral and systemic hemodynamics in the 2 groups. Generally the admittance rate of patients with malignant hypertension in the Netherlands is fairly small, and for practical reasons a sequential drug protocol was used. In spite of this study design, patient groups were fully comparable for anthropomorphic data.

Baseline cerebral and cardiovascular variables before treatment were not statistically different or fully identical. Importantly, baseline Doppler-derived flow velocity does not reveal volume flow, whereas, in this study, MCA Vmean before drug treatment did not differ significantly between groups. For methodologic reasons we restricted the interpretation by considering only changes in MCA Vmean with reference to baseline when comparing the circulatory effects of both drugs. More importantly, the dynamic CA capacity before treatment and the magnitude of BP reduction were almost identical, leaving the main findings of this study unchallenged.

Clinical Perspectives

Both SNP and labetalol reduce BP adequately in patients with malignant hypertension. However, the underlying systemic hemodynamic mechanisms are different. The use of labetalol resulted in a proportional reduction in systemic and cerebral vascular resistances. SNP, on the other hand, reduced systemic rather than cerebral vascular resistance with a larger rate of reduction in middle cerebral artery blood velocity, suggesting a preferential blood flow to the low resistance systemic vascular bed rather than the cerebral vascular bed.

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Disclosures

None.

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