Impaired Cerebral Autoregulation in Patients With Malignant Hypertension

Rogier V. Immink, MD; Bert-Jan H. van den Born, MD; Gert A. van Montfrans, MD, PhD; Richard P. Koopmans, MD, PhD; John M. Karemaker, PhD; Johannes J. van Lieshout, MD, PhD

Background—In patients with a malignant hypertension, immediate parenteral treatment with blood pressure–lowering agents such as intravenous sodium nitroprusside (SNP) is indicated. In this study, we evaluated static and dynamic cerebral autoregulation (CA) during acute blood pressure lowering with SNP in these patients.

Methods and Results—In 8 patients with mean arterial pressure (MAP) >140 mm Hg and grade III or IV hypertensive retinopathy at hospital admission, middle cerebral artery blood velocity (MCA V) and blood pressure were monitored. Dynamic CA was expressed as the 0.1-Hz MCA Vmean to MAP phase lead and static CA as the MCA Vmean to MAP relationship during SNP treatment. Eight normotensive subjects served as a reference group. In the patients, the MCA Vmean to MAP phase lead was lower (30°±8° versus 58±5°, mean±SEM; P<0.05), whereas the transfer gain tended to be higher. During SNP treatment, target MAP was reached within 90 minutes in all patients. The MCA Vmean decrease was 22±4%, along with a 27±3% reduction in MAP (from 166±4 to 121±6 mm Hg; P<0.05) in a linear fashion (averaged slope, 0.82±0.15% cm·s⁻¹·% mm Hg⁻¹; r=0.70±0.07).

Conclusions—In patients with malignant hypertension, dynamic CA is impaired. An MCA Vmean plateau was not detected during the whole SNP treatment, indicating loss of static CA as well. This study showed that during the rapid reduction in blood pressure with SNP, MCA Vmean decreases almost one on one with MAP. (Circulation. 2004;110:2241-2245.)

Key Words: blood flow velocity • cerebrovascular circulation • hypertension • ultrasonics

In patients with malignant hypertension, immediate treatment with blood pressure (BP)–reducing agents such as intravenous sodium nitroprusside (SNP) or labetalol is indicated to limit cerebral, myocardial, and renal damage.1 In these patients with a mean arterial pressure (MAP) >140 mm Hg, the presence of grade III to IV retinopathy and occasionally hypertensive encephalopathy, reflecting cerebral hyperperfusion and edema, is considered to indicate compromised cerebral autoregulatory capacity.2,3 From this assumption, it has become generally accepted that the initial reduction in blood pressure with SNP, MCA Vmean decreases almost one on one with MAP.

Cerebral autoregulation (CA) is defined as the intrinsic capacity of cerebral vasculature to maintain constant cerebral blood flow (CBF).7-9 In normotensive subjects, when MAP decreases below ≈60 mm Hg, considered the lower limit of CA, CBF decreases proportionally with BP. Most patients suffering from malignant hypertension have a history of chronic hypertension,10 and in those patients, the lower limit of CA has been shifted in proportion toward higher pressures.11,12 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 Hg13 in normotensive baboons and between 155 and 170 mm Hg in chronic hypertensive baboons.14

A moderate reduction in BP with SNP in normotensive subjects does not influence CBF,15 but to the best of our knowledge, no human studies specifically tested the assumption that CA is impaired in patients with malignant hypertension. Therefore, we determined CA in this group of patients before and during a decline in BP elicited by SNP.

Methods

Subjects

Eight consecutive patients fulfilling the World Health Organization criteria for malignant hypertension, namely severely elevated blood pressure plus grade III (bilateral retinal hemorrhages or cotton wool exudates; n=5) or IV (III plus papilledema; n=3) hypertensive retinopathy according to the Keith, Wagener, and Barker classification, were included in the study (Table 1).

Before hospital admission, 3 of these 8 patients were known to have had moderate hypertension treated with 1 or 2 antihypertensive drugs. Two of these 3 patients withdrew medication without con-
sulting their general practitioners. One had untreated hypertension, 1 was normotensive, and the other 3 had undocumented BP.

At hospital admission, 3 of 8 patients presented with symptoms of hypertensive encephalopathy (eg, convulsions before hospital admission). Six patients had left ventricular hypertrophy, 6 had moderately elevated plasma creatinine levels (between 100 and 200 μmol · L⁻¹), and 1 had considerably elevated (1050 μmol · L⁻¹) plasma creatinine level. A cause of hypertension was identified in 3 patients: high-dose corticosteroid treatment, a cortisol-producing adrenal carcinoma, and deterioration of renal function with volume overload related to IgA nephropathy. In 5 patients, extended testing, including renal artery Doppler ultrasound, was performed to identify the causes of hypertension. In 2 others, BP was well controlled (BP, <120/80 mm Hg) with 2 antihypertensive drugs and tapering of corticosteroid dosage. Four patients were well controlled (BP, <140/90 mm Hg) with 3 or 4 antihypertensive drugs. In 2 others, BP was moderately elevated (BP, 150/90 mm Hg and 160/100 mm Hg) despite the use of 3 and 5 drugs, respectively. All subjects, or a direct relative in case of encephalopathy, received verbal and written explanation of the objectives and techniques of measurements and risks and benefits associated with the study. They provided written informed consent in accordance with the Helsinki Declaration. This study was approved by the Medical Ethics Committee of the Academic Medical Center, University of Amsterdam (the Netherlands; MEC 02/194).

### Measurements

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of Reference Subjects and Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference Subjects</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>(n=8)</td>
</tr>
<tr>
<td>M/F</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Height, cm</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>HR, bpm</td>
</tr>
<tr>
<td>BP, mm Hg</td>
</tr>
<tr>
<td>Systolic</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Diastolic</td>
</tr>
<tr>
<td>MCA V, cm · s⁻¹</td>
</tr>
<tr>
<td>Maximum</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Minimum</td>
</tr>
<tr>
<td><strong>Values are mean (range).</strong></td>
</tr>
<tr>
<td>*P&lt;0.01 vs reference subjects.</td>
</tr>
</tbody>
</table>

placed at heart level. Stroke volume (SV) was determined by a 3-element model of arterial input impedance (Modelflow). Modelflow computes a flow wave from the FinAP wave that is integrated to obtain the SV of the heart. When calibrated against a “gold standard” method to determine cardiac output (CO) such as thermodilution or the Fick method, this methodology provides accurate estimates of changes in SV in patients with septic shock and cardiovascular disease and during orthostatic stress. The middle cerebral artery blood velocity (MCA V) was measured in the proximal segment of the right MCA (Multidop X4). Once the optimal signal-to-noise ratio was obtained, the probe was secured with a headband (Mark 600, Spacelabs Medical Inc). SNP was administered with a perfusor (B. Braun Medical Inc).

### Data Analysis

The signals of IAP, FinAP, and MCA V and a marker signal were A/D converted at 100 Hz and stored on a hard disk for offline analysis. In the patients, all signals were monitored from 20 minutes before SNP infusion to 1 hour after the last increment of SNP dose. Measurements were obtained in the reference subjects in the supine position for 30 minutes. MCA V (MCA Vmean), mean IAP, and mean FinAP were integral over 1 heartbeat. Heart rate (HR) was the inverse of the interbeat pressure interval; cardiac output (CO) was the product of SV and HR; and systemic vascular resistance (SVR) was mean IAP divided by CO. Because Modelflow was not calibrated, SV, CO, and SVR were expressed as percentage of the presenting value. To assess the effect of SNP on cerebrovascular conductance, a cerebrovascular conductance index was calculated as MCA Vmean divided by mean IAP. Changes in systemic and cerebral hemodynamics elicited by SNP were expressed as averages of 3-minute episodes of mean IAP, HR, SV, CO, SVR, MCA Vmean, and cerebrovascular conductance index determined at 3 moments: before SNP treatment, midway through treatment, and when target BP was reached.

For maintaining CBF, both fast- and slow-acting regulatory mechanisms are required to span the prevailing demands on CBF in everyday life.

Static CA (sCA) reflects overall efficiency of the autoregulation system and is assessed by monitoring the CBF during different levels of BP. Because changes in CBF are tracked by changes in MCA Vmean, sCA is considered intact when MCA Vmean barely changes during a decrease in IAP. To assess dCA for individual subjects in this study, the continuous signals of MCA Vmean and IAP were first averaged to 30-second episodes and then linearly related to each other.

Dynamic CA (dCA) refers to the ability to restore CBF in the face of a sudden change in perfusion pressure and reflects the latency of the system. It is quantified by the counterregulatory capacity to maintain constant MCA V during an induced or spontaneous abrupt changes in BP. In healthy subjects, MCA Vmean leads MAP with ~2.5 seconds in the time domain and ~60° in the frequency domain around the 0.1-Hz spontaneous BP variability. In this study, dCA was determined in the frequency domain from 3-minute episodes of beat-to-beat data of mean FinAP and MCA Vmean before SNP treatment and after target BP was reached. These data were compared with dCA in reference subjects determined in the supine resting state. To quantify the variability of pressure and velocity, power spectra were computed for mean FinAP and MCA Vmean with discrete Fourier transform after spline interpolation and resampling at 4 Hz of the beat-to-beat data sets. 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 mean FinAP and MCA Vmean coherence was used to signify that the 2 cardiovascular signals covary significantly at a given frequency. The squared coherence function reflects the fraction of output power (MCA Vmean) that can be linearly related to the input power (mean FinAP) at each frequency. Like a correlation coefficient, it varies between 0 and 1. From the mean FinAP to MCA Vmean cross spectrum, the transfer function gain (cm · s⁻¹ · mm Hg⁻¹) and the MCA Vmean to mean FinAP phase lead (degrees) were obtained in the low-frequency range.
TABLE 2. dCA in Reference Subjects and Patients

<table>
<thead>
<tr>
<th></th>
<th>Reference Subjects (n=8)</th>
<th>Before SNP</th>
<th>During SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP power, mm Hg$^2$·Hz$^{-1}$</td>
<td>4.5 (1.5–10.4)</td>
<td>5.8 (1.4–15.8)</td>
<td>11.3 (2.6–22.8)</td>
</tr>
<tr>
<td>V$_{max}$ power, (cm·s$^{-2}$)$^2$·Hz$^{-1}$</td>
<td>3.6 (1.1–9.8)</td>
<td>1.8 (1.1–4.9)</td>
<td>4.7 (0.9–9.1)</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.75 (0.54–0.84)</td>
<td>0.64 (0.49–0.76)</td>
<td>0.73 (0.48–0.91)</td>
</tr>
<tr>
<td>Phase, °</td>
<td>58 (41–82)</td>
<td>30 (6–67)*</td>
<td>42 (4–91)</td>
</tr>
<tr>
<td>Gain, %·%$^{-1}$</td>
<td>1.02 (0.48–1.37)</td>
<td>1.32 (0.93–1.87)</td>
<td>1.29 (1.00–1.70)</td>
</tr>
</tbody>
</table>

MAP power indicates low-frequency mean MAP variability; $V_{max}$, power, MCA $V_{mean}$ variability. Data are presented as mean (range).

*P<0.05 vs reference subjects.

The main findings of this study are that both dCA and sCA are impaired in patients with malignant hypertension before and during treatment with SNP. The data of this study show that during a rapid reduction in BP with SNP, MCA $V_{mean}$ decreases almost one on one with MAP.

Discussion

The technique to monitor changes in arterial CBF may raise discussion for several reasons. First, MCA $V_{mean}$ is calculated from the frequency distribution of the Doppler shifts, and it is assumed to represent flow velocity in the center of the vessel. Changes in MCA $V_{mean}$, however, reflect changes in flow only when the diameter of the MCA remains constant during SNP treatment. Direct observations made during craniotomy have revealed that SNP did not affect the vessel diameter of the M1 segment of the MCA; therefore, we consider that changes in MCA $V_{mean}$ in this study are proportional to those in flow.

Second, it is uncertain at which level of MAP the upper and lower limits of sCA are located in patients (admitted to hospital) with malignant hypertension. In normotensive humans, the lower limit of sCA is located ≈60 mm Hg. For obvious reasons, the upper limit of sCA cannot be studied in (normotensive) humans, but in normotensive baboons, it ranges between 120 and 150 mm Hg. In humans with untreated severe chronic hypertension, the lower limit of sCA

![Figure 1. BP response to SNP. Averaged decrease in mean IAP during SNP treatment of 8 subjects with malignant hypertension before and during treatment with SNP.](http://circ.ahajournals.org/)

Figure 1. BP response to SNP. Averaged decrease in mean IAP during SNP treatment of 8 subjects with malignant hypertension. Values are mean±SEM.
sCA and dCA

Autoregulation implies that blood flow is maintained at a normal level of \( \approx 60 \text{ mL} / \text{100 g brain tissue per minute} \) despite changes in perfusion pressure.7 Impaired sCA, with loss of the more-or-less zero-slope MAP–MCA V mean relationship, has been reported in ischemic stroke,34 in severe head injury,35 and after cardiac arrest.36 Our findings suggest that sCA also is impaired in patients with malignant hypertension.

dCA is quantified by the counterregulatory capacity to maintain MCA V during abrupt changes in BP induced by thigh cuff deflation25 or as evaluated by the transfer gain and phase lead of MCA V mean to MAP during imposed37 or spontaneous BP oscillations.38,39 During both hypotension8 and hypertension,26 this phase lead remains unaltered compared with the normal situation. In the present study, the MCA V mean to MAP phase lead in patients with malignant hypertension before SNP treatment was significantly smaller than in the reference subjects and comparable to the phase lead found in patients with carotid artery obstruction.37 The tendency toward a larger transfer gain further supports a deteriorated dampening of BP oscillations in patients with malignant hypertension.

SNP and Cerebral Hemodynamics

Kety et al40 observed that, in chronically hypertensive patients, global resting CBF and cerebral oxygen consumption are not different from those in normotensive subjects but that cerebrovascular resistance is elevated. SNP reduces SVR, but when infused directly in the carotid artery, it does not modify cerebrovascular resistance in healthy subjects.41 These findings, together with recent evidence that in normotensive subjects a reduction in MAP by SNP does not affect MCA V mean,32 suggest that when BP is reduced pharmacologically, MCA V is secured by CA-mediated cerebral vasodilatation rather than a direct SNP-induced pharmacological effect on
the cerebral vasculature. The present data demonstrate systemic vasodilatation during SNP treatment with a considerable increase in CO but no change in the cerebrovascular conductance index. One may speculate that the linear relation between MAP and MCA Vmean during treatment with SNP reflects a preferential blood flow to the (low-resistance) systemic vascular bed versus the (high-resistance) cerebrovascular bed.

In conclusion, in patients with malignant hypertension, dCA is impaired. Decreases in cerebral artery blood velocity and BP in a linear fashion during SNP treatment also indicate impairment of sCA. This study confirms the contention that CA is compromised in patients with malignant hypertension.

Acknowledgment

This study was sponsored in part by grant 98.172 from the Dutch Heart Foundation.

References

Impaired Cerebral Autoregulation in Patients With Malignant Hypertension
Rogier V. Imming, Bert-Jan H. van den Born, Gert A. van Montfrans, Richard P. Koopmans, John M. Karemaker and Johannes J. van Lieshout

_Circulation._ 2004;110:2241-2245; originally published online October 4, 2004;
doi: 10.1161/01.CIR.0000144472.08647.40
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/110/15/2241

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/