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Chapter 9

Central versus peripheral blood pressure in malignant hypertension; effects of antihypertensive treatment

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Submitted
ABSTRACT

Introduction Sodium nitroprusside and labetalol are recommended for the immediate treatment of malignant hypertension. Both intravenous agents have different effects on systemic hemodynamics and they might have differential effects on pulse wave reflection and pulse pressure amplification with consequences for peripheral versus central blood pressures.

Methods We studied 8 patients treated with sodium nitroprusside (44±14 yrs, 6 males, 225±22/135±8 mmHg) and 6 patients with intravenous labetalol (39±15 yrs, 4 males, 232±22/138±17 mmHg) before and after treatment, aiming at a 25% reduction in mean arterial pressure. We measured peripheral pressures using an intra-arterial catheter in the radial artery and derived central pressures by a generalized transfer filter.

Results Mean arterial pressure was similarly reduced with sodium nitroprusside and labetalol (27 and 30 %, \( p=0.76 \)). There was a non-significant greater reduction in peripheral systolic blood pressure with labetalol compared to sodium nitroprusside (29±11 vs 18±7 %, \( p=0.08 \)). The decline in peripheral diastolic pressure was comparable, whereas the reduction in peripheral pulse pressure was 8±16 % with sodium nitroprusside and 33±17 % with labetalol (\( p=0.01 \)). The decline in reflection magnitude was larger with sodium nitroprusside than labetalol treatment. There were no significant differences in central blood pressure reduction. Pulse pressure amplification increased with sodium nitroprusside, but did not change with labetalol.

Conclusion We found no difference in central systolic and pulse pressure between sodium nitroprusside and labetalol, whereas labetalol gave a greater reduction in peripheral systolic and pulse pressure during the immediate treatment of malignant hypertension.
INTRODUCTION

Malignant hypertension is a hypertensive emergency defined by a severe elevation of blood pressure accompanied by bilateral grade III and IV retinopathy according to the Keith, Wagener and Barker classification. Patients with malignant hypertension should receive immediate antihypertensive treatment, because of high risk of renal failure, stroke, myocardial infarction and heart failure. However, this should be done with caution since in malignant hypertension cerebral autoregulation, which is the capacity of the cerebral vasculature to maintain a stable cerebral blood flow, is impaired and during an acute lowering of blood pressure, middle cerebral artery blood velocity decreases considerably. Immediate reductions in mean arterial pressure (MAP) of more than 50% have been associated with cerebral ischemia, stroke and death. Therefore, to prevent hypoperfusion of the brain, the consensus is to pursue a MAP reduction of no more than 25% in the acute phase. Sodium nitroprusside (SNP) and labetalol are recommended as first line therapy for the immediate treatment of malignant hypertension. Both intravenous agents are effective in lowering blood pressure, but have different effects on systemic hemodynamics: SNP, a nitric oxide donor, lowers blood pressure mainly by decreasing systemic vascular resistance, while cardiac output is increased because of increase in heart rate without a significant change in stroke volume. With labetalol, a selective α1-adrenergic and a nonselective β-adrenergic receptor antagonist, the reduction in systemic vascular resistance is modest, with a decline in cardiac output by a reduction in heart rate.

Clinically, treatment is guided by blood pressure measurements from an intra-arterial catheter placed in the radial artery. It has been recognized, however, that antihypertensive drugs differ in their capacity to lower central blood pressure, while their effects on peripheral blood pressure may be similar. Vasodilatory antihypertensive drugs such as calcium channel blockers and angiotensin converting enzyme inhibitors lower central blood pressure more than thiazide diuretics and (first and second generation) beta blockers despite similar reductions in peripheral blood pressure. These differences are attributed to differential effects on heart rate and systemic vascular resistance causing altered wave reflection patterns. To our knowledge, the differential effects of antihypertensive drugs on peripheral and central blood pressures have not been studied in malignant hypertension.

We therefore assessed the effects of SNP and labetalol on peripheral and central systolic and pulse pressures and on pulse wave reflection and pulse pressure amplification during treatment of patients with malignant hypertension, while aiming at 25% reduction in MAP.
METHODS

Study design and treatment

We studied 14 patients fulfilling the WHO criteria for malignant hypertension: severely elevated blood pressure accompanied by grade III or IV hypertensive retinopathy according to the Keith, Wagener and Barker classification. All patients were admitted to the medium care unit of the Academic Medical Center, Amsterdam, for intravenous treatment and continuous blood pressure monitoring in the radial artery. Aiming at a MAP reduction of approximately 25% below the presenting value, the first 8 patients were treated with SNP and the last 6 patients were treated with labetalol. The treatment protocol has been described previously. In short, SNP infusion was started at 0.3 μg/kg/min, increased to 0.5 μg/kg/min after 5 minutes and, from then on, by 0.5 μg/kg/min every 5 minutes until target MAP was reached (with a maximum of 5 μg/kg/min). Labetalol was administered as bolus of 0.5 mg/kg every 8 minutes with a maximum of 200 mg. When the desired MAP was reached, a continuous infusion of 20 mg/hour was given. All patients gave written informed consent. The study was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam.

Hemodynamic measurements

Peripheral systolic (pSBP), diastolic (pDBP), pulse pressure (pPP) and mean arterial pressure (MAP) were measured with an intra-arterial catheter (1.1-mm ID, 20 gauge) placed in the radial artery. We compared a 3 minute interval of hemodynamic data at baseline to the instant when the desired reduction in MAP was reached. Central aortic systolic (cSBP) and pulse pressure (cPP) were derived off-line with a generalized pressure transfer filter as previously described. Since peripheral and central values for MAP and DBP are more or less similar, we only report peripheral MAP and DBP. Pulse pressure amplification (PPA) was defined as pPP/cPP. Waveform separation by dedicated software programmed in Mathematica (Wolfram Research, Inc., Mathematica, Version 4.0, Champaign, IL) was applied on the calculated central aortic pressure waves to derive forward (Pf) and backward pressure (Pb) waves. Reflection magnitude (RM), as a measure of wave reflection, was the ratio of the amplitudes of Pb and Pf.

Statistical analysis

Baseline data are expressed as mean plus standard deviation (SD) for continuous variables and as n (%) for categorical variables. Because of the small sample size we conservatively used non-parametric tests. Within-treatment group differences between baseline and end of treatment were tested using Wilcoxon signed rank test. Since blood pressures before treatment differed between the treatment groups, we normalised the baseline data and compared calculated percent changes in outcome parameters compared them to baseline. The Wilcoxon rank sum test was used to assess percent changes between the SNP and labetalol treatment group. We
considered a $p$-value < 0.05 significant. Data were analysed using SPSS software version 16.0.1 (SPSS Inc., Chicago, Illinois, USA).

## RESULTS

### Baseline characteristics

Baseline characteristics are shown in table 1. There were no significant differences in age, sex, BMI and blood pressure between the SNP and labetalol treated groups at baseline.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SNP</th>
<th>Labetalol</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>44±14</td>
<td>39±15</td>
<td>0.57</td>
</tr>
<tr>
<td>Male, no (%)</td>
<td>6 (75)</td>
<td>4 (67)</td>
<td>0.73</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24±2</td>
<td>25±4</td>
<td>0.62</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>225±22</td>
<td>232±22</td>
<td>0.95</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>135±8</td>
<td>138±17</td>
<td>0.85</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>162±11</td>
<td>170±18</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Data are means with standard deviation (SD) or otherwise specified. Abbreviations: SNP=sodium nitroprusside; BMI=body mass index; SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure.

### Peripheral and central blood pressures

Table 2 shows the absolute blood pressures before and after treatment. The reduction in MAP was similar with SNP and labetalol (27 vs 30 %, $p=0.76$). All peripheral and central blood pressures parameters significantly decreased compared to baseline during treatment with SNP and labetalol. In figure 1 percent changes in peripheral and central systolic and pulse pressure are shown for both treatment groups. There was a trend towards a greater reduction in pSBP with labetalol compared to SNP (29±11 vs 18±7 %, $p=0.08$). pPP declined by 8±16 % with SNP and 33±17 % with labetalol ($p=0.01$). The change in DBP was not different between SNP and labetalol (25±8 vs 27±11 %, $p=0.76$). For central blood pressure there were no significant differences between SNP and labetalol. cSBP decreased by 27±9 % in the SNP treatment group compared to 29±11 % in the labetalol treatment group ($p=0.76$); for cPP the decrease was 35±11 and 34±18 % respectively ($p=0.85$). PPA increased by 0.5±0.3 after SNP, while it did not change after labetalol. In both treatment groups RM decreased significantly from baseline to after treatment. The decline in RM was larger with SNP than labetalol treatment (0.24±0.1 vs 0.07±0.1, $p<0.01$).
Table 2 Peripheral and central blood pressures before and after treatment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SNP Before</th>
<th>SNP After</th>
<th>Labetalol Before</th>
<th>Labetalol After</th>
</tr>
</thead>
<tbody>
<tr>
<td>pSBP, mmHg</td>
<td>222±20</td>
<td>182±15*</td>
<td>233±18</td>
<td>164±27*</td>
</tr>
<tr>
<td>pPP, mmHg</td>
<td>102±19</td>
<td>91±13*</td>
<td>95±13</td>
<td>64±21*</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>121±18</td>
<td>91±18*</td>
<td>138±16</td>
<td>101±12*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>156±16</td>
<td>114±16*</td>
<td>169±18</td>
<td>119±15*</td>
</tr>
<tr>
<td>HR, min⁻¹</td>
<td>86±20</td>
<td>104±18*</td>
<td>98±20</td>
<td>72±13*</td>
</tr>
<tr>
<td>cSBP, mmHg</td>
<td>204±23</td>
<td>148±11*</td>
<td>202±17</td>
<td>144±25*</td>
</tr>
<tr>
<td>cPP, mmHg</td>
<td>79±19</td>
<td>50±7*</td>
<td>66±10</td>
<td>44±16*</td>
</tr>
<tr>
<td>PPA</td>
<td>1.3±0.3</td>
<td>1.8±0.2*</td>
<td>1.5±0.2</td>
<td>1.5±0.2</td>
</tr>
<tr>
<td>RM, %</td>
<td>0.69±0.1</td>
<td>0.45±0.1*</td>
<td>0.67±0.1</td>
<td>0.60±0.2*</td>
</tr>
</tbody>
</table>

Table 2 shows mean±SD peripheral and central blood pressures before and after treatment with sodium nitroprusside (SNP) and labetalol. Abbreviations: p=peripheral, c=central, SBP=systolic blood pressure, DBP=diastolic blood pressure, PP=pulse pressure, MAP=mean arterial pressure, HR=heart rate, PPA=pulse pressure amplification, RM=reflection magnitude. * p<0.05 before vs after treatment.

Figure 1
Percentage change ±SD in peripheral systolic blood pressure (pSBP), peripheral pulse pressure (pPP), central systolic blood pressure (cSBP) and central pulse pressure (cPP) for sodium nitroprusside in black and labetalol in grey bars.
DISCUSSION

The treatment of malignant hypertension calls for immediate lowering of blood pressure. Guidelines advice to lower MAP by 25%, because larger reductions of MAP have been associated with symptomatic hypoperfusion of the brain, resulting in cerebral damage and even death. A new finding is that during the treatment of malignant hypertension, aiming at a 25% reduction in MAP, there were no differences in central systolic and pulse pressure between labetalol and SNP. In contrast, labetalol gave a greater reduction in peripheral systolic and pulse pressure than treatment with SNP. Pulse pressure amplification therefore increased with SNP, but not with labetalol. One explanation for this phenomenon is that with SNP wave reflection decreased, while there was no change with labetalol.

We previously showed that in the treatment of malignant hypertension SNP decreases systemic vascular resistance with 43%, while for a similar blood pressure reduction labetalol lowers systemic vascular resistance by 13% and lowered cardiac output by reducing heart rate. In the current study we show that these differences in hemodynamics did not lead to differences in percent change in cSBP and cPP when aiming at a 25% reduction in MAP. There were however differences in peripheral blood pressure: labetalol lowered pSBP and pPP more than SNP.

Differences in peripheral and central blood pressure lowering capacity between antihypertensive drug classes are attributed to differential effects on heart rate and systemic vascular resistance causing altered wave reflection patterns. In the Conduit Artery Function Evaluation (CAFE) study, randomisation between the beta-blocker/thiazide diuretic based treatment and calcium channel blockers/angiotensin converting enzyme inhibitors showed similar reductions in peripheral blood pressures, while the latter treatment regimen provided lower central blood pressures. Moreover, the treatment group receiving calcium channel blockers/angiotension converting enzyme inhibitors showed a significant reduction in major cardiovascular endpoints compared to the beta-blocker/thiazide diuretic based treatment regimen. Evidence is mounting that central blood pressure has better predictive value of organ damage and cardiovascular mortality. Ochi and colleagues showed that central systolic blood pressure but not peripheral blood pressure was associated with cerebral small vessel disease. Also, central systolic blood pressure was better at predicting white matter lesions that peripheral systolic blood pressure. In malignant hypertension cerebral autoregulation is impaired and systemic blood pressure reductions are transferred to cerebral blood flow almost one on one, thus supporting the clinical relevance of effects of antihypertensive agents on arterial pulse wave reflection. PPA as the ratio of pPP and cPP decreased during SNP treatment, but not with labetalol. Since cPP was equally lowered with the two treatment modalities, the difference in PPA seems largely attributable to the change in pPP. PPA is the physiological phenomenon that describes the increase in pulse pressure from central to peripheral arteries, because of regional differences in arterial compliance. Both the increase in PPA and the decrease in RM during SNP treatment likely reflect the decrease in systemic vascular resistance and/or the increase in heart rate, since
it has been shown that PPA and wave reflection are heart rate dependent.\textsuperscript{18, 19} Depending on the choice of antihypertensive agents, peripheral arterial pressure do not fully appreciate central pulsatile blood pressure components. In the labetalol group, the proportional reduction in peripheral and central PP can be appreciated form the unchanged PPA. On the other hand, when treatment with SNP would have been targeted at SBP, central pressure would have been lower than desired because of the increase in PPA. Since in this study treatment was targeted at MAP this was not a clinical problem.

Besides in malignant hypertension, cerebral autoregulation is also impaired in ischemic stroke\textsuperscript{20} and preeclampsia,\textsuperscript{21} clinical conditions that require prompt blood pressure lowering treatment. Current recommendations for stroke and pre-eclampsia however are targeted at reducing peripheral systolic blood pressure. When targeting peripheral blood pressure central blood pressure, as a surrogate of cerebral perfusion pressure, might unintentionally be lowered even further, depending on the antihypertensive agent used. Under the conditions of impaired cerebrovascular autoregulatory capacity a reduction in blood pressure may provoke cerebral hypoperfusion.

**Limitations** The following points merit consideration. For obvious reasons treatment with labetalol and SNP cannot be blinded and randomised for. Furthermore, inherent to the incidence of malignant hypertension, patient groups were small with some differences in baseline blood pressure between treatment groups. Importantly, the relative reduction in MAP with labetalol versus SNP was of comparable magnitude, enabling to adequately compare the cardiovascular effects.

**Conclusion** During the immediate treatment of malignant hypertension, while aiming at a 25% MAP reduction, we found no differences in central systolic and pulse pressures between SNP and labetalol. However, with labetalol, but not SNP, central blood pressure is well reflected by peripheral blood pressure because PPA and RM did not change. So, depending on the choice of antihypertensive drug central pulsatile blood pressure components are not fully appreciated when looking at peripheral pressures. This may be relevant when choosing blood pressure targets for antihypertensive therapy, especially in situations where cerebral autoregulation is impaired.
REFERENCES
