Nitroprusside in Preeclampsia
Circulatory Distress and Paradoxical Bradycardia

Nathan Wasserstrum

In severe preeclampsia, short-term peripartum management of hypertension with hydralazine is complicated by relatively prolonged hypotensive episodes, resulting in fetal distress. We hypothesized that nitroprusside's rapid onset and brief antihypertensive action would permit more controlled blood pressure reduction. Nitroprusside was infused into 10 invasively monitored subjects until mean arterial pressure either 1) was gradually reduced 10–20% or 2) fell abruptly. Subjects fell into two groups, defined by whether the hypotensive effect of nitroprusside was accompanied by a fall in heart rate (group A, n=8) or a rise (group B, n=2).

Group B showed the expected sinoaortic baroreceptor reflex elevations in heart rate (+17 ±6 beats/min) in response to moderate falls in mean arterial pressure (−32±9 mm Hg) elicited by moderate doses (1.03±0.23 μg/kg/min). However in group A, steep reductions in mean arterial pressure (−75±22 mm Hg, p<0.0001), significantly greater than in group B (p<0.05), occurred at much lower doses (0.35±0.23 μg/kg/min; p<0.05) and were accompanied by falls in heart rate (−21±7 beats/min). The apparently paradoxical falls in heart rate and extreme hypotensive responses in group A indicate severe circulatory compromise, corresponding to the cardiac and vasomotor depression that characterizes severe hemorrhage and other forms of acute/severe hypovolemic hypotension. This hemodynamic pattern represents a cardiopulmonary baroreceptor reflex presumably related to the Bezold-Jarisch reflex. The appearance of this pattern in the present study probably reflects the imposition of nitroprusside's prominent venous dilator action on the relatively reduced blood volume that generally characterizes severe preeclampsia.

Preeclampsia, a hypertensive disorder unique to pregnancy, occurs in about 7% of pregnancies that continue beyond the first trimester. Severe preeclampsia is distinguished from the mild form of the disease by the magnitude of hypertension (severe, systolic pressure greater than 160 mm Hg or diastolic pressure greater than 110 mm Hg) and the existence or severity of proteinuria, visual symptoms, pulmonary edema, epigastric pain, or other accompanying disturbances. Severe preeclampsia is a major cause of maternal and fetal morbidity and mortality. Its etiology has not been established.

The reduced sinoaortic baroreceptor reflex sensitivity that characterizes severe preeclampsia results in hemodynamic instability. This instability, manifested as markedly enhanced responses to antihypertensive drugs, is of concern with hydralazine because of the relatively long and variable intervals to its maximum effect and its relatively long durations of action. When cumulative doses of the drug exert their full effects without baroreceptor reflex buffering, severe hypotension and fetal distress frequently results.

Intravenous nitroprusside has become the drug of choice for parenteral treatment of most hypertensive crises in nonpregnant adults and has largely supplanted diazoxide and hydralazine in that setting. We hypothesized that nitroprusside, because of its rapid onset and short duration of action, would lead to more controlled short-term reduction in blood pressure in severe preeclampsia than is possible with hydralazine.

Our results, including identification of a characteristic pattern of severe hypotension and apparently paradoxical fall in heart rate, pertain not only to the drug's potential clinical use but also yield insights into the pathophysiology of circulatory control in severe preeclampsia.

Methods

Women suffering from severe preeclampsia in the third trimester of pregnancy with a mean arterial pressure (MAP) greater than 130 mm Hg and with greater than 1+ proteinuria were studied. Patients...
were excluded if 1) they had been undergoing chronic antihypertensive therapy or had taken any antihypertensive or potentially vasoactive agent in the previous 24 hours; 2) they had preexisting cardiac disease; 3) there was evidence at entry of fetal distress or imminent delivery. Consecutive patients who were admitted to the Obstetric Intensive Care Unit and satisfied entry criteria were studied.

The mean age of the 10 women enrolled was 22.7±4.4 years; the gestational age of the pregnancies was 32.9±3.9 weeks. Seven of the 10 patients were nulliparous. The protocol was approved by the Baylor Institutional Review Board for Human Research and was used only after informed consent of the individual subject was obtained. Each subject received an initial loading dose followed by continuous intravenous infusion of magnesium sulfate at 2-3 g/hr. At least 2 hours passed between the loading dose and collection of data. Five percent dextrose in lactated Ringer's solution was administered at a rate of 75 ml/hr.

The radial artery was cannulated. Percutaneous catheterization of the pulmonary artery with a flow-directed catheter (Swan-Ganz, Edwards Laboratories, Anasco, Puerto Rico) was performed. Catheter position during insertion was determined by pressure waveform analysis and subsequently confirmed by a single anterior-posterior chest x-ray. As customary, a wedge was kept under the patient's right hip throughout the study to avoid vena caval compression. The mid axillary line served as the zero reference level.

Systolic and diastolic arterial pressure, MAP, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and heart rate (HR) were recorded on a polygraph (Hewlett-Packard, Palo Alto, Calif.). Pulse pressure was calculated as systolic minus diastolic pressure.

An intravenous infusion of nitroprusside was begun at 0.02 µg/kg/min, with incremental increases in dosage until a 10-20% reduction in MAP was reached. Infusion was immediately stopped at the onset of any abrupt reduction in pressure. Data at baseline and blood pressure nadir were analyzed.

Among the 10 subjects, a subset of eight (group A) experienced frank reductions in HR (−21±7 beats/min, p<0.0001, t test) in association with the falls in blood pressure. This subset, defined by reductions in HR, will be referred to as group A. The other two subjects, in whom heart rate rose during the hypotensive episode (+17±6 beats/min), comprised group B.

Subjects in group A (defined by reductions in HR), experienced very steep falls in blood pressure onto the polygraph. For these and CVP measurements, respiratory fluctuations were identified on the polygraph record and measurements were taken at end expiration. Unless otherwise specified, results are reported as mean±SD.

Statistical analysis of paired data was by paired t test. For part of the analysis, patients were divided into two subgroups (group A, n=8; group B, n=2), defined by a fall (group A) or rise (group B) in HR during nitroprusside infusion. Statistical comparisons between the two groups were made via the two-sample Wilcoxon rank-sum test. A value of p<0.05 was taken as significant for both tests.

Results

Nitroprusside lowered blood pressure in all 10 subjects (Table 1). Regression analysis of the data for the full set of subjects indicated that changes in MAP and HR were directly (not inversely) related (r=0.7652; p<0.005, t test). Similarly, the lower an individual patient's nadir MAP, the lower was her concomitant HR (Figure 1) (r=0.8365; p<0.005, t test).

Among the 10 subjects, a subset of eight (group A) experienced frank reductions in HR (−21±7 beats/min, p<0.0001, t test) in association with the falls in blood pressure. This subset, defined by reductions in HR, will be referred to as group A. The other two subjects, in whom heart rate rose during the hypotensive episode (+17±6 beats/min), comprised group B.

Subjects in group A (defined by reductions in HR), experienced very steep falls in blood pressure

| Table 1. Mean Hemodynamic Measurements for Full Set of 10 Patients |
|-----------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Stats           | Base MAP | Nadir MAP | Base PuPr at MAP nadir | Base PuPr | Base syst | Nadir syst | Base dias | Nadir dias | Base HR | HR at MAP nadir | Base CVP | Base PCWP | Dose (µg/kg/min) |
| Mean±SD         | 150     | 86*     | 82     | 44†    | 205     | 110*     | 123     | 66*     | 97     | 84     | 6.1     | 11.5     | 0.49     |
| MAP, mean arterial pressure (mm Hg); PuPr, pulse pressure (mm Hg); syst, systolic arterial pressure (mm Hg); dias, diastolic arterial pressure (mm Hg); HR, heart rate (beats/min); CVP, central venous pressure (mm Hg); PCWP, pulmonary capillary wedge pressure (mm Hg); SD, standard deviation. *
p<0.0001, †p<0.001, paired t test, comparing base with nadir.

![Figure 1. Scatterplot shows direct correlation of nadir mean arterial pressure (MAP) with concomitant heart rate (HR).](http://hyper.ahajournals.org/DownloadedFrom)
Paradoxical Bradycardia in Preeclampsia

(-75±22 mm Hg, p<0.0001, t test) (Figure 2). In contrast, in group B the falls in MAP were more moderate (-32±9 mm Hg) and significantly smaller than those in group A (p<0.05, Wilcoxon).

Group B demonstrated the smoothly controlled reductions in blood pressure sought in the study. In contrast, hypotensive episodes in group A began abruptly. In some subjects in group A, heart rate during the interval preceding the abrupt depressor response was higher than its control, preinfusion value (Figure 2).

The marked hypotensive responses in group A occurred at very low doses of nitroprusside (0.35±0.23 µg/kg/min). In contrast, the milder hypotensive response in group B occurred at doses (1.03±0.23 µg/kg/min) that were significantly higher than those administered in group A (p<0.05, Wilcoxon, Table 2).

For the full set of 10 patients, baseline CVP averaged 6.1±3.8 and PCWP 11.5±4.7 (Table 1). Nadir values of MAP and the concomitant HR and the magnitudes of change in MAP and HR were not related to baseline CVP or PCWP. Groups A and B were not distinguishable on the basis of their respective baseline hemodynamic measurements. When the infusion was stopped, MAP and HR returned rapidly toward control values in both groups.

Four patients in group A experienced severe nausea near the MAP nadir. No patient in either group required cesarean section for fetal distress related to a hypotensive episode.

Discussion

In nonpregnant subjects, the fall in MAP produced by vasodilator administration elicits a compensatory

| Table 2. Statistical Comparison of Group A With Group B |

<table>
<thead>
<tr>
<th>Stats</th>
<th>Base MAP</th>
<th>Nadir MAP</th>
<th>Base PuPr</th>
<th>PuPr at MAP nadir</th>
<th>Base syst</th>
<th>Nadir syst</th>
<th>Base dias</th>
<th>Nadir dias</th>
<th>Base HR</th>
<th>HR at MAP nadir</th>
<th>Base CVP</th>
<th>Base PCWP</th>
<th>Dose (µg/kg/min)</th>
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<tr>
<td>Group A (n=8)</td>
<td>152</td>
<td>78*</td>
<td>84</td>
<td>42</td>
<td>208</td>
<td>101*</td>
<td>124</td>
<td>59*</td>
<td>100</td>
<td>79</td>
<td>6.7</td>
<td>11.7</td>
<td>0.35*</td>
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<tr>
<td>Group B (n=2)</td>
<td>143</td>
<td>112</td>
<td>74</td>
<td>51</td>
<td>193</td>
<td>145</td>
<td>119</td>
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<tr>
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Inclusion in group A is defined by a fall in heart rate. Inclusion in group B is defined by a rise in heart rate. Standard deviations (SD) for CVP and PCWP are absent for group B because baseline central pressure measurements could only be obtained in one of the two patients in this group. MAP, mean arterial pressure (mm Hg); PuPr, pulse pressure (mm Hg); syst, systolic arterial pressure (mm Hg); dias, diastolic arterial pressure (mm Hg); HR, heart rate (beats/min); CVP, central venous pressure (mm Hg); PCWP, pulmonary capillary wedge pressure (mm Hg).

*p<0.05, two sample Wilcoxon rank sum test comparing group A with group B. For MAP, PuPr, syst, dias, and HR, the change (i.e., the difference between base and nadir) produced by infusion is compared for the two groups. For CVP, PCWP, and Dose, absolute value is compared for the two groups.
baroreceptor reflex rise in HR. Thus, HR varies inversely with MAP. Similarly, in severe preeclampsia, the hypotensive responses to vasodilators such as hydralazine and diazoxide are accompanied by elevations in HR. Because sinoaortic baroreceptor reflex sensitivity is reduced in severe preeclampsia, the reflex elevations in HR in response to acute vasodilator-induced hypotension may be very small. However, frank reductions in HR in response to arterial vasodilators have not been reported in severe preeclampsia.

In contrast, in the present study, eight subjects (group A) of 10 exhibited frank reductions in HR during the hypotensive response to nitroprusside. Such “paradoxical” reductions in HR are not explainable in terms of the sinoaortic baroreceptor reflex.

Despite the abrupt and steep hypotensive response produced by nitroprusside, MAP and HR returned rapidly toward control levels when the infusion was stopped. This reflects the drug’s short half-life. Thus, unlike the experience reported with hydralazine, no patient in the present study required cesarean section for fetal distress related to a hypotensive episode.

In nonpregnant patients in hypertensive crisis, titration of nitroprusside dosage generally permits well-controlled reductions in blood pressure. A final dose of 1.0–3.0 μg/kg/min is usually required. In contrast, in group A the mean dose at which abrupt hypotensive episodes occurred was only 0.35 μg/kg/min.

Group B showed results more consistent with the literature. Moderate, well-controlled reductions in MAP occurred at significantly higher doses than in group A and were accompanied by the expected baroreceptor reflex increases in HR.

Mechanism

The apparently anomalous results in group A help elucidate the circulatory pathophysiology of severe preeclampsia. Their interpretation is facilitated by consideration of two points.

1) There are some well-defined circumstances under which acute hypotension is accompanied by a fall in HR. These include the supine hypotension syndrome of pregnancy, the Bezold-Jarisch reflex, and reflexive cardiac and vasomotor depression elicited by severe hemorrhage and other forms of acute/severe hypovolemic hypotension.

2) Although hydralazine and diazoxide relax only arterial resistance vessels, nitroprusside also relaxes venous capacitance vessels. Thus, although all three drugs produce hypotensive responses, only nitroprusside can, under appropriate conditions, also produce functional hypovolemia.

Supine Hypotension

The supine hypotensive syndrome is defined by marked reductions in MAP and HR that occur in a small percentage of late gestation gravida when they adopt the supine position. The position produces caval compression and a reduction in venous return, thereby leading to a fall in MAP. Shortly after MAP starts to fall, reflex reduction in HR begins.

Depending on baseline hemodynamic status, nitroprusside may increase or decrease cardiac output. In the context of the abnormally reduced blood volume characteristic of untreated severe preeclampsia, nitroprusside-induced venodilation decreases venous return and cardiac output. This potentiates the fall in MAP produced by the drug’s arterial vasodilator action. Thus, the fall in HR we observed in group A may reflect a mechanism similar to that responsible for the supine hypotensive syndrome.

Of interest, in the supine hypotensive syndrome, HR frequently rises before beginning its abrupt fall. This is analogous to the responses of some subjects treated with nitroprusside (Figure 2). In both instances, the initial rise in HR probably reflects activation of the sinoaortic baroreceptor reflex before the latter is overpowered by an increasingly severe hypovolemic and hypotensive stimulus.

Cardiac and Vasomotor Depression Due to Ventricular Reflexes

Strictly defined, Bezold-Jarisch effects are reflex responses elicited from inferior ventricular receptors by ischemia or by various compounds, including prostaglandins, that are locally secreted in response to ischemia. The reflex results in hypotension (vasomotor depression) and a fall in HR (cardiac depression). The Bezold-Jarisch reflex, even defined so strictly, cannot be excluded as the mechanism underlying the fall in HR and severe hypotension demonstrated by group A.

Indeed, the bradycardia associated with nitroprusside may be at least in part due to stimulation of prostaglandin biosynthesis in the heart. In pentobarbital-anesthetized rats, retrograde injection of nitroprusside in the thoracic aorta produced hypotension and bradycardia. Indomethacin abolished the bradycardia without reducing nitroprusside’s hypotensive effect. Thus, nitroprusside appeared to stimulate myocardial prostaglandin biosynthesis and thereby initiate a reflex bradycardia. Severe preeclampsia may be accompanied by a disturbance in cardiac prostaglandin synthesis that contributes to the greater sensitivity to nitroprusside noted in the present study. More generally, the importance of pharmacological effects on cardiac inhibitory reflexes has recently been emphasized.

Depressor reflexes also originate at other ventricular sites and in response to stimuli not necessarily related to ischemia. Data from a variety of models indicate that severe hemorrhage and other forms of severe hypovolemia and hypotension stimulate ventricular receptors (including mechanoreceptors) that elicit centrally mediated cardiac and vasomotor depressor reflexes.

When rats were bled to reach a predetermined MAP within 2 minutes, HR rose as long as MAP remained above 100 mm Hg. However, when MAP...
fell below 90 mm Hg, HR fell in proportion to the depth of hypotension. In humans, Barriot and Riou found that paradoxical bradycardia developed in 20 of 273 patients with acute hemorrhagic shock. Compared with the other patients, these 20 had more rapid and severe hemorrhage. Sander-Jensen et al reported that in patients monitored during resuscitation from hemorrhagic shock, mean HR was lower during the shock phase than during the steady state reached after volume repletion. This group of investigators also demonstrated that in healthy men, central hypovolemia induced via exposure to lower body negative pressure initially led to mild hypotension and relative tachycardia. After further exposure, a much greater fall in blood pressure was accompanied by a slowing of HR back to control levels. These depressor reflexes are sometimes categorized under more broadly defined Bezold-Jarisch effects. Recently, their role in cardiovascular regulation in various physiological and pathological states has become more widely appreciated.

Nitroprusside’s venodilator action combines with the abnormally reduced baseline blood volume of severe preeclampsia to produce severe functional hypovolemia and hypotension. This hemodynamic pattern is analogous to, and elicits the depressor reflex characteristic of, severe hemorrhage. This depressor pattern is reflected in the paradoxical fall in HR and abrupt, severe fall in MAP encountered in the present study.

Venous Tone

The maintenance of relatively normal central pressures and cardiac function in the face of a variably reduced blood volume is consistent with the concept of increased venous tone and central redistribution of blood volume in preeclampsia. In the presence of minimal baseline venomotor tone, a venodilator has minimal hemodynamic effect. Conversely, the marked response to nitroprusside-induced venodilation in the present study strongly supports the concept of high baseline venous tone in severe preeclampsia.

According to this view, patients in group A had a lower blood volume and greater venous tone than those in group B. This view is not contradicted by the absence of differences between groups A and B in central pressure or other baseline hemodynamics, or by the absence of any correlation between central pressures and the hemodynamic response to nitroprusside. Rather, it must be emphasized that the baseline hemodynamic indexes usually measured, including central pressures, simply do not yield an accurate assessment of venous tone.

Previous Reports of Venodilators in Preeclampsia

In contrast to our findings, previous investigators have reported control and stabilization of MAP with nitroprusside in severe preeclampsia that was apparently uncomplicated by abrupt, steep hypotensive episodes. Unfortunately, HR measurements for comparison with our results were not reported. The apparent conflict with our results is resolved when one notes that all five patients in the aforementioned studies were clinically in acute pulmonary edema before nitroprusside was administered. PCWP measurements reported on four of the five patients ranged from 20 to 33 mm Hg, consistent with increased rather than decreased baseline intravascular volume. Thus, these patients would not be expected to show the steep hypotension and paradoxical fall in HR that accompanies severe hypovolemic hypotension. In contrast, none of our patients showed evidence of elevated cardiac filling pressures or pulmonary edema.

Although not quite as powerful a vasodilator as nitroprusside, nitroglycerin acts more specifically on the venous capacitance beds. Thus, to the extent that the venodilator action of nitroprusside is responsible for the steep hypotension and paradoxical fall in HR we found in severe preeclampsia, one would expect to find analogous results with nitroglycerin. Careful reading of the published results on the hemodynamic effects of nitroglycerin in severe preeclampsia reveals a subset of patients with a pattern of hypotension and paradoxical fall in heart rate analogous to those we encountered with nitroprusside.

In conclusion, clinically the current results emphasize how poorly patients with preeclampsia compensate for hypovolemic stimuli such as venodilators or perioperative hemorrhage. Secher and Bie warned that in hemorrhage, “the concept of tachycardia, being the only deviation of heart rate... may be fatal to the patient if as a consequence a decrease in heart rate is interpreted as an improvement of the patient’s general condition.” Our results indicate that this warning applies as well to the patient with severe preeclampsia exposed to nitroprusside, hemorrhage, or other hypovolemic/hypotensive stimuli. Clearly, the use of nitroprusside in severe preeclampsia must be approached with caution and only after consideration of the patient’s blood volume.

The hemodynamic response to nitroprusside in the present study emphasizes that severe preeclampsia is characterized by decreased blood volume and increased venous tone. Thus, concomitant venous and arterial dilatation with nitroprusside frequently result in hypovolemic hypotension and severe circulatory compromise. The hypovolemic hypotension in turn elicits a pattern of reflex cardiac and vasomotor depression analogous to that seen in severe hemorrhage. The result is a fall in HR, and an abrupt, further fall in MAP. This reflects much more severe circulatory compromise than that caused by the decreased baroreceptor reflex sensitivity that characterizes severe preeclampsia.

References

KEY WORDS • blood pressure • blood volume • heart rate • pregnancy-induced hypertension • preeclampsia • bradycardia • reflex • pressoreceptors • hypovolemia • baroreceptor reflex
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N Wasserstrum

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