
Nitroglycerin Induced Hypotension Will Maintain CBF in Hypertensive Rats

WILLIAM E. HOFFMAN, PH.D., RONALD F. ALBRECHT, M.D., AND DAVID J. MILETICH, PH.D.

SUMMARY Cerebrovascular effects of intravenous (iv) nitroglycerin (NTG) infusions were tested in four month old spontaneously hypertensive rats (SHR) and Wistar Kyoto controls (WKY). Cerebral blood flow (CBF) changes were measured during iv NTG infusion in ventilated, halothane anesthetized rats using radioactive microspheres. In control WKY rats given isotonic saline infusions instead of NTG, blood pressure and CBF did not change over 3 microsphere injections. When blood pressure was decreased to 65 and then 45 torr with iv NTG infusions, CBF was maintained or increased in both SHR and WKY. There was no difference in response between SHR and WKY. These results support other reports that NTG has direct cerebrovasodilating effects, and indicate that this action will maintain adequate CBF in hypertensive as well as normotensive subjects to pressures below 50 torr.

DURING CHRONIC arterial hypertension there is an impairment of cerebral autoregulation. In normotensive subjects cerebral blood flow (CBF) may be maintained down to mean blood pressures of 60–70 torr, but CBF may decrease at pressures above 100 torr in hypertensive subjects. Impaired cerebral autoregulation has also been identified in spontaneously hypertensive rats (SHR). It is often desirable and necessary to control hypertension during intraoperative periods and to induce hypotension to reduce blood loss. Reductions in blood pressure increases the risk of cerebral ischemia in hypertensives more than in normotensive subjects. One possible solution to this problem is the use of a hypotensive drug which also has direct cerebrovasodilating effects. Nitroglycerin (NTG) is a drug which has been suggested for use in hypotensive anesthesia. This drug also has been reported to reverse cerebrovasospasm. Although cerebrovasodilation has been reported during NTG induced hypotension, other reports have indicated that NTG treatment increases intracranial pressure and may decrease CBF. In these experiments the cerebrovascular effects of NTG induced hypotension were studied in anesthetized spontaneously hypertensive rats (SHR) and normotensive Wistar Kyoto controls (WKY).

METHODS

Surgery

Male SHR and WKY, (4 months old) were used in these experiments. One experiment was performed in the morning and one in the afternoon. Rats from each of the 3 groups, sham treated WKY (n = 13), NTG treated WKY (n = 10), NTG treated SHR (n = 12), were tested in a randomized order. All rats were implanted with PE50 femoral artery and vein catheters and a left ventricle catheter implanted via the right carotid artery under 1.5% halothane anesthesia according to previously described methods. A tube was inserted into the trachea and used for artificial ventilation. Respiratory rate was 48 min⁻¹ and tidal volume was adjusted between 3 to 4 ml using a Harvard small animal respirator in order to obtain an arterial pCO₂.
of 35–40 torr. Following the completion of all surgery, the inspired halothane concentration was adjusted to 0.5% in 100% oxygen and maintained at the level for 30 minutes prior to the start of testing. Throughout the experiment the rats were paralyzed with 1 mg/kg • hr tubocurare.

**Experimental protocol**

Cerebral blood flow was measured in these experiments with radioactive microspheres. The methods used for microsphere injection and tissue blood flow analysis have been described previously. Each rat received 3 microsphere injections. The 15μ microspheres used for these experiments were labelled with cobalt-57, ruthenium-103, and scandium-46. A group of WKY received 3 microsphere injections under control conditions. The first microsphere injection was given under control conditions. The second and third microsphere injections were given during iv infusion of isotonic saline at a rate of 0.2 ml per minute. These animals were used as treatment controls. Arterial pCO₂ was maintained at 35–40 torr and body temperature at 37°C as in experimental rats. Thirty minutes were allowed between microsphere tests.

In NTG treated SHR and WKY the first microsphere injection was given under control anesthetized conditions. The second microsphere injection was given during an NTG infusion which decreased mean blood pressure to 65–70 torr in both groups of rats. The third microsphere injection was given during iv NTG infusions which decreased mean blood pressure to a range of 40–50 torr. Each hypotensive level was stabilized and maintained for 5 minutes before the microsphere injection. The rats were allowed 30 minutes between test periods in order to allow the blood pressure to recover and stabilize between NTG infusions. The NTG used in these experiments was dissolved in isotonic saline at a concentration of 1 mg/ml. The mean blood pressure and NTG infusion rate was noted immediately before the start of the microsphere test in order to calculate cerebral vascular resistance (CVR = mean blood pressure/CBF). All rats were sacrificed at the end of each experimental protocol. After the rat was sacrificed, the whole brain was dissected out and placed in 10% formalin. The following day the brain was blotted dry and weighed. The activity of each labelled microsphere was analyzed using a Nuclear Chicago 1085 gamma counter and a Nuclear Data 600 multichannel analyzer.

**Statistics**

Data are reported as mean ± SE. NTG treatment groups were compared with an interdata computer using a repeated measures analysis of variance (BMDP, UCLA, California) and paired and unpaired t-tests.

**Results**

Changes in blood gases, blood pressure, CBF and CVR during NTG treatment in anesthetized SHR and WKY are shown in Table. During halothane anes-

**Discussion**

It is known that cerebral autoregulation is impaired in hypertensive subjects. CBF may decrease and signs of cerebral ischemia may become apparent at mean blood pressures of 100 torr or higher in chronically hypertensive subjects. Infusion of NTG maintained or increased CBF even under conditions of relatively severe hypotension (40–50 torr). In addition, CVR and CBF changes were similar between SHR and WKY during NTG induced hypotension. These data support the conclusion that vasodilator induced hypotension provides for better maintenance of CBF than during hypotension produced by ganglionic blockade or hemorrhage.

NTG is a direct vasodilating drug which has been recently introduced as an alternative drug to sodium nitroprusside (SNP) for controlled hypotension during anesthesia and for congestive heart failure. It has also been used in the treatment of cerebral vasospasm. The cerebrovascular effects of SNP and NTG induced hypotension have been compared in enflurane anesthetized rats. It was shown that at similar hypotensive pressure levels (approximately 60 torr), CBF was maintained with NTG treatment but decreased significantly during SNP infusion. Stoyka and Schutz found that SNP maintained CBF down to very low blood pressures. However, Michenfelder and Theye reported that SNP induced hypotension to levels of 50 to 60 torr in dogs resulted in a significant decrease in CBF. Miletich et al. also found decreases in CBF in goats when blood pressure was lowered to 42 torr using SNP. In SHR, we found no evidence that SNP improved the lower limit of cerebral autoregulation to the extent observed here. The evidence suggests that SNP may have direct cerebrovasodilatory effects, but it does not alter cerebral autoregulation to the extent observed here with NTG.
TABLE  
Arterial Blood Gases and pH, Blood Pressure, Cerebral Blood Flow, Cerebral Vascular Resistance, and Nitroglycerin Infusion Rates in Halothane Anesthetized SHR and WKY (mean ± se)

<table>
<thead>
<tr>
<th></th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTG treated SHR (n = 12)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>$pCO_2$ (torr)</td>
<td>36 ± 2</td>
<td>37 ± 2</td>
<td>40 ± 2</td>
</tr>
<tr>
<td>$pO_2$ (torr)</td>
<td>274 ± 26</td>
<td>290 ± 21</td>
<td>256 ± 21</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 ± 0.02</td>
<td>7.37 ± 0.01</td>
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<tr>
<td>Mean blood pressure</td>
<td>155 ± 5</td>
<td>78 ± 4*</td>
<td>46 ± 2*</td>
</tr>
<tr>
<td>Cerebral blood flow</td>
<td>62 ± 9</td>
<td>108 ± 13*</td>
<td>65 ± 7</td>
</tr>
<tr>
<td>(ml/min-100g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral vascular resistance (torr/ml/min-100g)</td>
<td>3.24 ± 0.61</td>
<td>0.69 ± 0.07*</td>
<td>0.79 ± 0.08*</td>
</tr>
<tr>
<td>Nitroglycerin infusion rate (mg/kg-min)</td>
<td>0</td>
<td>0.28 ± 0.09</td>
<td>1.40 ± 0.20</td>
</tr>
<tr>
<td>NTG treated WKY (n = 10)</td>
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<td></td>
<td></td>
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<tr>
<td>$pCO_2$</td>
<td>37 ± 1</td>
<td>41 ± 2</td>
<td>41 ± 2</td>
</tr>
<tr>
<td>$pO_2$</td>
<td>309 ± 13</td>
<td>310 ± 11</td>
<td>288 ± 9</td>
</tr>
<tr>
<td>pH</td>
<td>7.40 ± 0.01</td>
<td>7.38 ± 0.02</td>
<td>7.37 ± 0.03</td>
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<tr>
<td>Mean blood pressure</td>
<td>130 ± 6</td>
<td>67 ± 1*</td>
<td>42 ± 1*</td>
</tr>
<tr>
<td>Cerebral blood flow</td>
<td>68 ± 8</td>
<td>83 ± 10*</td>
<td>58 ± 7</td>
</tr>
<tr>
<td>(ml/min-100g)</td>
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<td></td>
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<tr>
<td>Cerebral vascular resistance</td>
<td>2.22 ± 0.21</td>
<td>0.96 ± 0.16*</td>
<td>0.80 ± 0.13*</td>
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<tr>
<td>Nitroglycerin infusion rate</td>
<td>0</td>
<td>0.37 ± 0.15</td>
<td>1.36 ± 0.11</td>
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<tr>
<td>Sham treated WKY (n = 13)</td>
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<tr>
<td>$pCO_2$</td>
<td>38 ± 1</td>
<td>38 ± 1</td>
<td>41 ± 1</td>
</tr>
<tr>
<td>$pO_2$</td>
<td>299 ± 17</td>
<td>292 ± 23</td>
<td>293 ± 27</td>
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<tr>
<td>pH</td>
<td>7.43 ± 0.12</td>
<td>7.43 ± 0.16</td>
<td>7.40 ± 0.12</td>
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<tr>
<td>Mean blood pressure</td>
<td>130 ± 6</td>
<td>131 ± 5</td>
<td>128 ± 6</td>
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<tr>
<td>Cerebral blood flow</td>
<td>74 ± 7</td>
<td>74 ± 7</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>(ml/min-100g)</td>
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<td></td>
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<tr>
<td>Cerebral vascular resistance</td>
<td>1.83 ± 0.18</td>
<td>1.85 ± 0.14</td>
<td>1.97 ± 0.19</td>
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<tr>
<td>Nitroglycerin infusion rate</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*p < 0.05 compared to test 1 in each rat, paired t test.

SHR were significantly hypertensive compared to WKY under control conditions ($p < 0.05$). CVR was significantly elevated in SHR under control conditions compared to sham treated but not NTG treated WKY. No other values were significantly different under control conditions.

In summary, results presented here indicate that the cerebrovasodilating effects of NTG are adequate to maintain CBF in normotensive and hypertensive rats with a mean blood pressure as low as 30% of control levels. This may be contrasted with the effects of ganglionic blockade in SHR. It was observed that decreasing mean blood pressure in SHR to 58% of control hypertensive levels with hexamethonium produced a significant decrease in CBF.

In summary, results presented here indicate that the direct cerebrovasodilating effects of NTG aid in the maintenance of CBF during moderate to severe hypotension (30–50% of control blood pressure). In addition, cerebrovascular responses of 4 month old SHR were similar to those observed in WKY at each hypotensive level. These data suggest NTG induced hypotension maintains adequate CBF in hypertensive subjects. This is in contrast to the effects of hypotension induced with hemorrhage, ganglionic blockade, or SNP infusion in hypertensive subjects. Lowering blood pressure with these treatments will produce significant decreases in CBF in hypertensive rats and humans at levels which are well within the cerebral autoregulatory range of normotensive subjects. These results suggest that while ganglionic blockade and SNP may have little effect on cerebral autoregulation in normotensive or hypertensive subjects, NTG enhances the cerebral vasodilatory effect of autoregulation, particularly in SHR.

**References**

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