Basilar Arterial Flow Changes Elicited by Hydralazine Hydrochloride, Isoxsuprine Hydrochloride and Nylidrin Hydrochloride

BY WILLIS K. MITCHELL, PH.D., AND WILLIAMINA A. HIMWICH, PH.D.

Abstract:
Basilar Arterial Flow Changes Elicited by Hydralazine Hydrochloride, Isoxsuprine Hydrochloride and Nylidrin Hydrochloride

The influence of infusion of hydralazine, isoxsuprine or nylidrin on blood flow in the basilar artery and on systemic blood pressure was investigated in anesthetized dogs. The drugs were administered individually in 1-mg and 2-mg doses and in various combinations of 1 mg each by injection just proximal to the formation of the basilar artery. Analysis of the data revealed significant increases in blood flow (P<0.05) immediately after injection and a statistically significant (P<0.05) interaction between time and drug. No statistical differences were found in comparisons of the effects of the 1-mg and 2-mg dose levels for any of the drugs. At either dosage isoxsuprine and nylidrin caused a 16% to 28% decrease in systemic blood pressure, while hydralazine effected a more moderate, approximately 5%, decrease. Basilar flow responded to 1-mg combinations of isoxsuprine/hydralazine and nylidrin/hydralazine with a consistent 25% to 30% increase. However, the flow response to nylidrin/isoxsuprine was unpredictable. The data indicate that these substances increased basilar arterial flow by inducing a transient local vasodilatation. The effects of the drug combinations on flow were in general synergistic and positive, and were similar to those after infusion of the individual drugs, except for a somewhat slower initial response and a longer duration.

Additional Key Words
- drug combinations
- vasoactive hydrochlorides
- blood pressure
- vasodilatation

The action of hemodynamically active substances has been investigated following their oral administration by estimating their peripheral segmental effects. The nitrous oxide technique has been used for the direct evaluation of the effects on cerebral circulation in subjects receiving the drugs by either the oral or the intravenous route. Moreover, except for a few of Eisenberg's patients, the subjects of these studies suffered from hypertension or cerebrovascular disease. In the experiments reported here, ostensibly normal animals were used to investigate the immediate effects on blood flow in the basilar artery of individual drugs and of drug combinations administered by intra-arterial infusion.

Methods
Forty-five adult mongrel dogs weighing an average of 17.3 kg, and maintained at a surgical level of anesthesia with pentobarbital sodium (30 mg/kg administered intravenously), were utilized in the experiments. A catheter inserted in the femoral artery was used to monitor the systemic blood pressure. The basilar artery was exposed via a ventrocervical approach by the removal of the ventral portions of the occipital and postpheno...
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segments of the axial skeleton. A cannula for drug injection was inserted in the spinomedullo circle just proximal to the confluence of the vertebral arteries to form the basilar artery. A standard 3-mm Model EP-702 blood flow transducer in conjunction with a Model 301 electromagnetic flowmeter (Carolina Medical Electronics, Inc., Winston-Salem, North Carolina) was used to measure basilar arterial flow, which was recorded simultaneously with the systemic blood pressure on a Type R Multichannel Dynograph (Offner Electronics, Inc., Chicago, Illinois). Drug administration was standardized so that 1 ml of fluid was injected during a 15-second interval and only one drug injection was given per animal, thus not adding significantly to the fluid volume in the vascular system. Physiological saline was utilized as the carrier for the drugs injected. In order to eliminate any possibility of the carrier medium creating a vasoactive response, identical volumes of saline at room temperature were injected into control animals. No evident changes in systemic blood pressure or basilar blood flow were noted with the saline injections. Probe calibration was accomplished by producing zero flow via mechanical occlusion, and subsequent integration by compensating polar planimeter (Keuffel & Esser Company, Morristown, New Jersey) on exact blood volume at the end of the experiment. Actual flow was then obtained by measuring zero occlusions against the calculated ml/mm of height.

A 2 X 3 x 3 split plot factorial statistical design9, 10 was used. The factors were dosage (1 and

<p>| TABLE 1A |
| Mean Flow Values and Standard Error of the Means for all Treatment Combinations* † |</p>
<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th>Control</th>
<th>After 10 sec</th>
<th>After 20 sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nylidrin</td>
<td>6.13 ± 1.26†</td>
<td>7.42 ± 1.47</td>
<td>7.01 ± 1.24</td>
</tr>
<tr>
<td>Isoxsuprine</td>
<td>7.07 ± 1.01</td>
<td>11.88* ± 1.71</td>
<td>9.95* ± 1.88</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>8.99 ± 0.97</td>
<td>12.76* ± 1.21</td>
<td>11.18* ± 1.18</td>
</tr>
<tr>
<td>1 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nylidrin</td>
<td>5.22 ± 1.73</td>
<td>7.51 ± 2.61</td>
<td>7.05 ± 2.46</td>
</tr>
<tr>
<td>Isoxsuprine</td>
<td>8.35 ± 1.06</td>
<td>13.04* ± 2.40</td>
<td>12.30* ± 2.19</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>8.51 ± 0.88</td>
<td>11.69* ± 1.36</td>
<td>10.47* ± 0.98</td>
</tr>
</tbody>
</table>

*Values within rows with different superscripts are significantly different (P < 0.05).
†Data in each row are a composite of five animals.
††Values given are in ml/min.

| TABLE 1B |
| Analysis of Variance for Blood Flow Values |

<table>
<thead>
<tr>
<th>Source</th>
<th>DF</th>
<th>ss</th>
<th>ms</th>
<th>cacl F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between subjects</td>
<td>29</td>
<td>1160.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (dose)</td>
<td>1</td>
<td>0.86</td>
<td>0.86</td>
<td>1</td>
</tr>
<tr>
<td>B (drug)</td>
<td>2</td>
<td>287.66</td>
<td>143.83</td>
<td>4.11*</td>
</tr>
<tr>
<td>AB</td>
<td>2</td>
<td>23.10</td>
<td>11.55</td>
<td>1</td>
</tr>
<tr>
<td>Subjects within groups error (between)</td>
<td>24</td>
<td>849.03</td>
<td>35.38</td>
<td></td>
</tr>
<tr>
<td>Within subjects</td>
<td>60</td>
<td>311.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C (time)</td>
<td>2</td>
<td>174.52</td>
<td>87.26</td>
<td>38.62†</td>
</tr>
<tr>
<td>AC</td>
<td>2</td>
<td>1.53</td>
<td>0.77</td>
<td>1</td>
</tr>
<tr>
<td>BC</td>
<td>4</td>
<td>24.06</td>
<td>6.01</td>
<td>2.66*</td>
</tr>
<tr>
<td>ABC</td>
<td>4</td>
<td>2.66</td>
<td>0.66</td>
<td>1</td>
</tr>
<tr>
<td>CX subjects within groups error (within)</td>
<td>48</td>
<td>108.47</td>
<td>2.26</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05.
†P < 0.01.
2 mg), drug (isoxsuprine, hydralazine and nyli- drin), and time (control, immediately after in- jection, and 30 seconds postinjection), respective- ly. This particular design permitted the detection and investigation of any interactions between the three factors involved.

**Results**

For all three drugs an increase in basilar arterial blood flow (ml/min) occurred in the time period immediately after injection and was still apparent 30 seconds after injection (table 1A). Analysis of the blood flow data (table 1B) revealed statistical differences in drug effects ($P < 0.05$) between the subjects. An analysis of within-subject data showed that the time factor was highly significant ($P < 0.01$) and that the interaction term of time with drug was also significant ($P < 0.05$), indicating that under the different drug treatments the patterns of change in basilar flow varied with time in a way that was not due to chance and that the two factors did not function independently of one another. This significant interaction be- tween drug and time indicated that an examination of the simple effects of the two time periods on the response to each drug was...
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necessary. Statistical differences were found for the time intervals following the administration of isoxsuprine (P < 0.01) and hydralazine (P < 0.05). Duncan’s multiple range test, which was employed to disclose statistical differences between means at each time interval within each drug, revealed that in the case of both isoxsuprine and hydralazine the means for the measurements immediately after injection and after 30 seconds were statistically different from the control values. It was found that at 30 seconds the flow values were returning toward the original control values, and that in general they were intermediate between control values and those immediately after injection.

Although with nylidrin differences in flow did not attain statistical significance, postinjection flow changes exhibited a pattern similar to that of isoxsuprine and of hydralazine. Isoxsuprine at 1-mg and 2-mg levels increased basilar blood flow to the greatest extent, 60.0% and 69.1%, respectively (fig. 1). Comparable values for hydralazine and nylidrin were 36.7% and 37.7%, and 37.7% and 22.2%, respectively. With either dose of the three drugs, at the 30-second interval blood flow values had begun to return toward control or preinjection levels (table 1A).

An immediate decrease in blood pressure (mm Hg), noted at both dosage levels for all three drugs, was least marked with hydralazine (table 2A). The analysis of variance indicated that the factor of drug between subjects was highly significant at the P < 0.01 level (table 2B).

Table 2A

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control</th>
<th>After 10 sec</th>
<th>After 30 sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nylidrin</td>
<td>135.0 ± 11.04†</td>
<td>108.5 ± 15.47</td>
<td>121.5 ± 4.54</td>
</tr>
<tr>
<td>Isoxsuprine</td>
<td>168.0 ± 10.52</td>
<td>141.5 ± 9.28</td>
<td>136.5 ± 8.77</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>145.5 ± 17.08</td>
<td>140.0 ± 17.23</td>
<td>141.0 ± 24.02</td>
</tr>
<tr>
<td>2 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nylidrin</td>
<td>151.0 ± 12.57</td>
<td>111.5 ± 19.89</td>
<td>100.5 ± 17.88</td>
</tr>
<tr>
<td>Isoxsuprine</td>
<td>154.0 ± 18.25</td>
<td>112.0 ± 20.87</td>
<td>119.5 ± 37.06</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>155.0 ± 8.48</td>
<td>140.0 ± 22.98</td>
<td>150.5 ± 8.95</td>
</tr>
</tbody>
</table>

*Data in each row are a composite of five animals.
†Values given are in mm Hg.

Table 2B

Analysis of Variance for Blood Pressure Values

<table>
<thead>
<tr>
<th>Source</th>
<th>DF</th>
<th>ss</th>
<th>ms</th>
<th>calc F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between subjects</td>
<td>29</td>
<td>29,066.63</td>
<td>525.63</td>
<td>1.00</td>
</tr>
<tr>
<td>A (dose)</td>
<td>1</td>
<td>525.63</td>
<td>525.63</td>
<td>1.00</td>
</tr>
<tr>
<td>B (drug)</td>
<td>2</td>
<td>9,191.25</td>
<td>4,595.67</td>
<td>6.67**</td>
</tr>
<tr>
<td>AB</td>
<td>2</td>
<td>2,828.75</td>
<td>1,414.37</td>
<td>2.05</td>
</tr>
<tr>
<td>Subjects within groups</td>
<td>24</td>
<td>16,521.00</td>
<td>688.37</td>
<td></td>
</tr>
<tr>
<td>error (between)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within subjects</td>
<td>60</td>
<td>689,614.00</td>
<td>6,055.83</td>
<td>1.00</td>
</tr>
<tr>
<td>C (time)</td>
<td>2</td>
<td>12,111.67</td>
<td>6,055.83</td>
<td>1.00</td>
</tr>
<tr>
<td>AC</td>
<td>2</td>
<td>846.66</td>
<td>423.33</td>
<td>1.00</td>
</tr>
<tr>
<td>BC</td>
<td>4</td>
<td>3,008.33</td>
<td>752.08</td>
<td>1.00</td>
</tr>
<tr>
<td>ABC</td>
<td>4</td>
<td>1,403.34</td>
<td>350.83</td>
<td>1.00</td>
</tr>
<tr>
<td>CX subjects within groups</td>
<td>48</td>
<td>6,672,244.00</td>
<td>139,005.08</td>
<td></td>
</tr>
<tr>
<td>error (within)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.01.
Duncan's multiple range test comparing the composite mean for each drug showed that the action of nylidrin was significantly different from that of isoxsuprine and of hydralazine.

Nylidrin, as well as isoxsuprine, had considerable reductive effects on mean blood pressure (fig. 2), and it was apparent when both dosage levels were considered that nylidrin was more efficacious than either of the other two drugs in decreasing blood pressure. In the case of hydralazine, a minor reduction in blood pressure of approximately 5% was noted. With isoxsuprine and hydralazine, but not with nylidrin, at a 1-mg dose this reduction was maintained until the termination of most experiments; at the 2-mg dose the duration of this effect was markedly enhanced by nylidrin and slightly augmented by hydralazine.

The mean flow values and standard error of the means for the drug combinations are shown in table 3. The analysis of variance for flow in the basilar artery when all possible combinations of the drugs were injected at a common dosage level of 1 mg disclosed that the only factor of significance was time within subjects (P < 0.01). The paired t test was also used to analyze changes in heart rate. Heart rate immediately after the injection of drugs was significantly different (P < 0.05) from heart rate before drug injection.

**Discussion**

In this study the drugs were infused directly into the arterial bed to determine their effects upon the cerebral vessels without the complications introduced by oral or intravenous administration. The variations in basilar blood
flow from animal to animal even under controlled conditions are of a magnitude that makes it desirable to use each animal as its own control. For this reason studies of the effects of the chronic administration of drugs were impractical. The results reported herein serve only to define the action of the drug on a cerebral artery.

Two weeks or more were required for cerebral blood flow in Eisenberg's patients to show a consistent response to nylidrin administration. In our studies on limited numbers of animals the intra-arterial injection (femoral artery) of 20 to 30 mg/kg of this drug had a slight depressant effect both on blood pressure and on flow (unpublished data). These data suggest that, in the case of nylidrin at least, a high blood level of the drug may be important. It may be that nylidrin when given orally is slowly or inefficiently eliminated (or metabolized) and gradually builds up in blood (and tissues) to an effective level or, alternately, that the drug is metabolized to a more active compound which in turn builds up slowly.

Certainly the cerebral blood vessels react to nylidrin as such with dilatation when it is presented to the arterial wall in the concentrations used in this study.

Results further indicate that isoxsuprine, hydralazine and nylidrin, when infused into the canine basilar artery, can markedly enhance blood flow in that vessel. This increase in basilar flow coincides in general with an immediate drop in systemic blood pressure and with a mild degree of tachycardia. Thus, the drugs apparently have similar vasodilatory effects on a localized area and also decrease vascular resistance and increase cardiac output, since a major fall in blood pressure did not occur in any of the animals. A previous report has indicated that with hydralazine cardiac output tends to rise unless the fall in blood pressure is extreme.

In our studies the increase in flow was immediate and apparently transient, for at 30 seconds it was generally subsiding toward normal flow levels. Thus, as the statistics of this study indicate and data from studies such as those of Rowe et al. support, time is a factor of paramount importance in the study and usage of these vasoactive substances. Time in the present study was shown to be of much greater importance than the dosage level of the drugs.

The percentage data (fig. 1) indicate that the 2-mg dosage of nylidrin surpassed the optimum level for eliciting a positive response via a sympathomimetic inhibitory pathway, since the flow increase was approximately 15.5% lower than that evoked by the 1-mg dose. This diminution in effect at the higher dosage level was not evident after the administration of 2 mg of isoxsuprine or hydralazine. Ablad and Johnsson found that hydralazine had a more pronounced vasodilatory effect on resistance vessels than did sodium nitrite. The reverse was true for capacitance vessels. Increases in blood volume and heart rate, as well as in cardiac output, were also produced by this drug. In view of the slight decrease in blood pressure with hydralazine it would seem that either stroke volume is decreased enough to account for the lowered pressure or that the effect of the drug on the resistance vessels is greater, and the vasodilation and increased heart rate are equilibrated to such a degree that only a slight drop in pressure results. The situation seems to be somewhat different with nylidrin and isoxsuprine since the pressure falls were considerably greater. Their immediate effect may be mediated more directly through decreasing peripheral resistance, thus increasing peripheral venous compliance to a degree which causes concomitant arterial pressure decreases, and allowing rapid flow of blood from the

---

**TABLE 3**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Control</th>
<th>After 10 sec</th>
<th>After 30 sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoxsupr/hydralazine</td>
<td>7.10 ± 2.54†</td>
<td>8.91 ± 1.84</td>
<td>9.64 ± 2.10</td>
</tr>
<tr>
<td>Nylidrin/hydralazine</td>
<td>7.66 ± 2.09</td>
<td>8.41 ± 1.53</td>
<td>8.54 ± 1.24</td>
</tr>
<tr>
<td>Nylidrin/isoxsuprine</td>
<td>8.20 ± 4.86</td>
<td>8.70 ± 5.73</td>
<td>10.96 ± 7.13</td>
</tr>
</tbody>
</table>

*Data in each row are a composite of five animals.
†Values given are ml/min.
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resistance to the capacitance area. This effect
would normally be of rather short duration
with the reduced pressure returning to normal
levels within a short period of time.

In examining the possibility of a synergis-
tic action between the drugs, no statistical
differences were found in the effects of
combinations of the drugs as compared with
those of the individual drugs. Evaluation of
the drug combinations revealed that flow 30
seconds after injection was significantly greater
than control values. The data indicate that the
flow increase was more linear and that
vasodilatation persisted for a longer time with
the drug combinations than with the individual
drugs. Of the three drug combinations, isoxsu-
prine/hydralazine and nylidrin/hydralazine ex-
hibited synergistic capabilities in prolonging
the duration of effects. Decreases in blood
pressure evoked by the drug combinations were
similar to those observed with the individual
drugs.

Analyses of hematocrit values obtained at
the beginning and ending of the experiments
yielded evidence of a hemoconcentration of
approximately 5% obtained at the termination.
This terminal increase in concentration was
quite consistent in all experimental animals.
The surgical procedures required an average of
three hours to perform, and therefore probably
much of the hemoconcentration could be
accounted for through simple fluid loss. Also,
excitement was found by Reece and Wahl-
strom14 to cause contraction of the spleen in
the canine and a resultant increase in cell
volume which lasted for as long as five
hours.

It has been considered that a primary
action of hydralazine in unanesthetized dogs15
and of nylidrin in patients16 is the production of
tachycardia. Tachycardia occurred following
the administration of both of these drugs in the
present experiment. The heart rate immediately
after injection was significantly increased
(P < 0.05) over control values. This effect
was somewhat transient and heart rate de-
creased to normal values within five minutes
postinjection.

Conclusions
Isosuprine and hydralazine significantly in-
creased blood flow in the basilar artery of the
dog. The increase in blood flow due to nylidrin
was not of sufficient magnitude to be statistical-
ly significant. Indications were that the vaso-
dilatory effects of the individual drugs were
transient, for, in general, return of flow and
pressure values toward preinjection levels was
seen at 30 seconds postinjection. These drugs
seemingly have an action on cerebral vascular
tone similar to that postulated for their action
in peripheral areas.2, 7, 10

An evaluation of a synergistic influence
indicated that, although combinations of the
drugs were somewhat slower in evoking a
vasodilatory response, the resulting vasodilata-
tion was longer in duration than that produced
by the individual drugs.

Acknowledgment
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Mrs. Norma Miller for their able assistance.

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sodium nitrite on blood flow and volume of
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