Effect of Nitroglycerin on Cerebral Circulation Measured by Transcranial Doppler and SPECT

Arve Dahl, MD, David Russell, MD, PhD, Rolf Nyberg-Hansen, MD, PhD, and Kjell Rootwelt, MD, PhD

We used a combination of transcranial Doppler ultrasonography and single-photon emission computed tomography to noninvasively assess changes in the diameter of the middle cerebral artery induced by sublingual nitroglycerin in 10 healthy subjects. Nitroglycerin reduced mean blood flow velocities without concurrently changing regional cerebral blood flow in the perfusion territory of this vessel. Our results strongly suggest that nitroglycerin causes vasodilatation of the basal intracranial arteries. (Stroke 1989;20:1733-1736)

Transcranial Doppler ultrasonography (TCD) is a new noninvasive examination method that enables the measurement of blood flow velocities in the basal intracranial arteries. The assessment of changes in velocity alone does not, however, provide direct information regarding changes in diameter if there is a concurrent change in blood flow through the artery. A combination of TCD examination of a particular major intracranial artery and measurement of regional cerebral blood flow (rCBF) in the perfusion territory of this vessel theoretically allows assessment of diameter changes since it may be assumed that each major intracranial artery supplies a defined weight of brain tissue. The aim of our study was to use these two methods to assess the effects of nitroglycerin on the diameter of the middle cerebral artery (MCA) and to determine if this substance causes changes in global or regional blood flow.

Subjects and Methods

Ten healthy volunteers (seven men and three women, aged 24-44 [mean 32.4] years) participated in the study. Blood flow velocity in the MCA and rCBF in the estimated perfusion territory of this vessel were measured before and after the sublingual administration of 1 mg nitroglycerin.

Blood flow velocity in the MCA was measured in all 10 subjects using a 2-MHz range-gated pulsed-wave Doppler instrument (TC2-64, EME, Uberlingen, FRG). The average time-mean velocity from 10 consecutive cardiac cycles, using the sampling depth giving the highest velocity (45-55 mm) was calculated for each subject. The Doppler examination was first carried out after the subject had rested quietly in the supine position for at least 10 minutes. After the administration of nitroglycerin, measurements were repeated every 2 minutes for 20 minutes and then every 5 minutes for a maximum of 120 minutes at the same depth in each subject.

In seven subjects, rCBF was measured before the administration of nitroglycerin and during the period of maximum mean MCA blood flow velocity reduction after the administration using xenon-133 inhalation and single-photon emission computed tomography (SPECT) (Tomomatic 64, Medimatic Inc., Copenhagen, Denmark). Measurements were made simultaneously in three 2-cm-thick brain slices which are routinely positioned 2, 6, and 10 cm above the orbitomeatal (OM) plane. Mean hemispheric blood flow and rCBF were calculated in milliliters per 100 grams brain per minute from Slice 2 (OM+6 cm) in a standardized region of interest in each hemisphere corresponding approximately to the estimated perfusion territory of the MCA. Blood pressure and end-expiratory Pco2 (CD-102 Normocap infrared CO2 analyzer, Datex Instrumentation Corp., Helsinki, Finland) were measured in all 10 subjects before and after the administration of nitroglycerin. Pco2 was recorded three times during the SPECT study: at the beginning, approximately half-way through, and at the end of the 4.5-minute examination period. The average of these three recordings was used for data analysis.

Reproducibility of the mean MCA blood flow velocity measurements was tested in an additional 20 healthy subjects who did not receive nitroglycerin, by
TABLE 1. Mean Middle Cerebral Artery Velocities, Mean Hemispheric and Regional Cerebral Blood Flow in the Middle Cerebral Artery Perfusion Territory, Pco2, and Blood Pressure Before and After Nitroglycerin Administration

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Before Nitroglycerin</th>
<th>After Nitroglycerin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA velocities (cm/sec) (n=10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>67±3.2</td>
<td>51±3.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Right side</td>
<td>63±3.2</td>
<td>46±2.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Both sides</td>
<td>65±3.2</td>
<td>48±2.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hemispheric CBF (ml/100 g/min) (n=7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>57±4.9</td>
<td>58±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Right side</td>
<td>58±4.9</td>
<td>59±3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Both sides</td>
<td>57±3.3</td>
<td>58±2.4</td>
<td>NS</td>
</tr>
<tr>
<td>MCA perfusion territory (ml/100 g/min) (n=7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>57±4.9</td>
<td>58±3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Right side</td>
<td>59±4.9</td>
<td>60±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Both sides</td>
<td>58±3.3</td>
<td>59±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Pco2 (mm Hg)</td>
<td>42.3±1.8</td>
<td>42.4±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>120/79</td>
<td>116/81</td>
<td></td>
</tr>
</tbody>
</table>

Values are given as mean±SEM. NS, not significant.

MCA, middle cerebral artery; CBF, cerebral blood flow.

repeating the TCD measurements on both sides within 1 hour.

The results are expressed as mean±standard error of the mean (SEM) except for the results of the reproducibility study, which are expressed as mean±standard deviation (SD). Changes after administration of nitroglycerin were analyzed by means of Wilcoxon's signed midrank test. Two-sided statistical tests were used. Changes were considered to be significant when \( p<0.05 \). Analysis of variance combined with correlation analysis and regression analysis were used to test reproducibility.

**Results**

Nitroglycerin caused a symmetric reduction in mean MCA blood flow velocities in all 10 subjects (Table 1). The reduction was highly significant when each side was studied separately (left side: \( 16±1.3 \) cm/sec, \( p<0.01 \); right side: \( 17±2.3 \) cm/sec, \( p<0.01 \)) and when both sides were considered together (\( 17±1.2 \) cm/sec, \( p<0.01 \)). Typical changes are shown in Figure 1. The reduction in mean MCA blood flow velocities was maximum 3-10 minutes after the administration of nitroglycerin and remained at this level for 31±8 (range 15-100) minutes. The biologic half-life of the effect on MCA blood flow velocities in eight subjects was 46±8 (range 25-90) minutes. In the other two subjects, the biologic half-life exceeded 120 minutes, our longest period of observation.

Mean hemispheric blood flow and rCBF in the MCA territory did not change significantly after the administration of nitroglycerin (Table 1). On the left side, for example, rCBF in the MCA perfusion territory was \( 57±4.9 \) ml/100 g/min before and \( 58±3.4 \) ml/100 g/min after administration. An example is shown in Figure 2. Blood pressure and end-expiratory Pco2 before the administration of nitroglycerin and at the time of maximum MCA blood flow velocity reduction were not significantly different (Table 1).

The analysis of reproducibility of the TCD method showed a difference between the two measurements of \( 0.4±3.2 \) cm/sec on the right and \( 1.7±3.0 \) cm/sec on the left. The correlation coefficient was 0.95. The reproducibility of the TCD method is therefore good when measuring mean MCA blood flow velocities.

**Discussion**

Blood flow (F) in a particular artery depends on the artery’s cross-sectional area (\( \pi r^2 \)) and the mean velocity (V) of the blood flowing through it as \( F=\pi r^2 \times V \). Using xenon-133 inhalation and SPECT, rCBF in the estimated perfusion territory of the MCA is measured in milliliters per 100 grams brain tissue per minute. Since the weight of brain tissue in the perfusion territory may be assumed to remain constant, relative changes in the diameter (\( \Delta \text{diam} \)) of the MCA after the administration of nitroglycerin are related to perfusion and mean blood flow velocity as

\[
\Delta \text{diam} = \left( \sqrt{\frac{r \text{CBF}_1}{r \text{CBF}_2}} \times \frac{V_1}{V_2} - 1 \right) \times 100
\]
where rCBF₁ and V₁ are the perfusion and velocity values before and rCBF₂ and V₂ are the perfusion and velocity values after administration of nitroglycerin, respectively. If, however, rCBF remains unchanged, the following equation is valid:

$$\Delta \text{diam} = \left( V_1 - V_2 \right) / V_2 \times 100.$$ 

The sublingual administration of 1 mg nitroglycerin did not cause changes in mean hemispheric blood flow or rCBF in the MCA perfusion territory. Blood flow velocities in the MCA did, however, decrease in all subjects without significant changes in Pco₂ or blood pressure. These findings strongly suggest that nitroglycerin causes vasodilatation of the MCA. Mean MCA blood flow velocities decreased by 25%, which represents a relative MCA diameter increase of 15%.

Nitroglycerin dilates both veins and arteries, with little effect on the smaller resistance vessels of the body.³ Although this drug is widely used as a coronary vasodilator in ischemic heart disease, knowledge regarding its effects on the large intracranial arteries in humans is limited. Animal studies using angiography have demonstrated nitroglycerin-induced vasodilatation of the large intracranial arteries in both monkeys and dogs.⁴ In vitro experiments have shown this effect to be more prominent in the proximal parts of the intracranial arteries.⁶ Cerebral blood flow in animals remained unchanged after doses of nitroglycerin causing a modest⁷ or a more marked⁸,⁹ reduction in blood pressure, suggesting that this substance does not alter normal cerebral autoregulation.

In humans an increase in intracranial pressure lasting 2–3 minutes has been observed following a bolus injection of 4 or 8 µg nitroglycerin/kg body wt; this increase in intracranial pressure was accompanied by a decrease in blood pressure.¹⁰ Similar findings have been reported in animals after a bolus injection.⁷,¹¹ Continuous infusion of nitroglycerin in animals, however, even in doses causing a decrease in blood pressure, has not caused an elevation of intracranial pressure.⁷

In our study the vasodilatory effect of nitroglycerin on the MCA was relatively long-lasting. This may suggest that the vasodilatation caused by this substance is more prolonged in the intracranial than in the extracranial arteries, a finding that has previously been observed in monkeys.⁴

In conclusion, our study strongly suggests that the combination of blood flow velocity and rCBF measurements may be used to noninvasively assess changes in the diameters of the basal intracerebral arteries. Furthermore, 1 mg nitroglycerin given sublingually causes a vasodilatation of the MCA without concurrent changes in mean hemispheric blood flow or rCBF in the perfusion territory of this vessel.

References


KEY WORDS • cerebral blood flow • ultrasonics • glyceryl trinitrate • vasodilation
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