Intravenous Nicardipine in Cats Increases Optic Nerve Head But Not Retinal Blood Flow

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The effect of intravenously injected nicardipine on retinal and optic nerve head (ONH) blood flow was studied in 27 cats using laser Doppler velocimetry and flowmetry, respectively. A dose of 20 μg/kg of nicardipine had little effect on retinal blood flow. A dose of 100 μg/kg, however, produced a significant transient decrease in flow. By contrast, both doses produced a significant increase in ONH blood flow despite a significant decrease of the mean arterial blood pressure. Measurements of the partial pressure of oxygen (PO₂) with an oxygen-sensitive microelectrode, whose tip was placed in the vitreous just in front of the optic disc, showed a significant increase in the PO₂ that paralleled the increase in ONH blood flow. These results demonstrate, for the first time to the authors’ knowledge, a pharmacologically induced increase in ONH blood flow and suggest that nicardipine could have a beneficial effect on ONH tissue. Invest Ophthalmol Vis Sci 33:2885–2890, 1992

Nicardipine, a derivative of dihydropyridine, is a potent vasodilator of cerebral vessels through its calcium-antagonistic action.1-3 It is used in the treatment of systemic hypertension and coronary insufficiency.4,5 This drug increases regional cerebral blood flow in anesthetized dogs1 and cats2 and cerebrocortical partial pressure of oxygen in cats.6 It has a longer stronger hypotensive effect than papaverine, and its effect on cerebral blood flow is also stronger (approximately 100-fold) than that of the latter.1

Although nicardipine might be an important drug in the treatment of retinal occlusive diseases, ischemic optic neuropathy, and glaucoma, studies of its effect on the retinal circulation have been few and limited to rabbits. An average dilation of retinal vessels of approximately 3% and 22% was found after intravenous administration of doses of 0.01 and 0.1 mg/kg, respectively.7 Because rabbits do not have truly retinal vessels, these results cannot be extrapolated to other species. For this reason, we did a study in anesthetized cats, which have a fully developed retinal circulation, and determined the effect of nicardipine on retinal and optic nerve head (ONH) hemodynamics.

Materials and Methods

Animal Preparation

Twenty-seven cats (weight range, 2.1–3.5 kg) were prepared as described in detail elsewhere8 using procedures that conformed to the ARVO Resolution on the Use of Animals in Research. Each cat was premedicated with atropine (0.04 mg/kg subcutaneously) and anesthetized with intramuscular ketamine hydrochloride (22 mg/kg) and acepromazine maleate (2 mg/kg). Catheters were placed in a femoral artery and vein, and a tracheostomy was done. A loading dose of pancuronium bromide (0.2 mg/kg) was administered intravenously, and the animal was ventilated with 21% O₂, 50% N₂O, and 29% N₂, using a variable volume respirator. Arterial mean blood pressure (BP), tidal CO₂, and heart rate were monitored continuously. Arterial pH, partial CO₂ pressure (Pco₂), and partial oxygen pressure (PO₂) were monitored intermittently using a blood gas analyzer. Adjustments of the inspired gas mixture, tidal volume, and respiration rate were made to keep the pH at approximately 7.4; Pco₂ at approximately 31 mmHg; PO₂ ≥ 90 mmHg; and arterial mean BP at 85–110 mmHg. Rectal temperature was maintained at approximately 38°C. Halothane (0.7–1.5%) was administered, and pancuronium bromide (0.15 mg/kg/hr) was infused continuously. The pupils were dilated with 1% tropicamide and 10% phenylephrine, and the cat was placed prone on a table with its head secured in a special clamp. A ring was sutured to the eye with three stitches at the limbus and

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held in a fixed position to prevent eye motion. A zero diopter contact lens was placed on the cornea that was protected with sodium hyaluronate.

**Relative Retinal Blood Flow**

Laser Doppler velocimetry was used in seven cats to determine the relative center-line velocity, $V_{max}$, of erythrocytes moving in retinal vessels. A laser Doppler fundus camera was placed in front of the eye. An area of 30° of the fundus was illuminated continuously in a range of wavelengths (500–570 nm), and the retina therefore was light adapted during the measurements. The beam from a laser diode (near-infrared light at 789 or 810 nm, approximately 100 μW at the cornea) was focused on a retinal arteriole, close to the disc. All light scattered by erythrocytes into the input pupil of the fundus camera was collected by a single optical fiber to detect the maximum amount of scattered light; this method maximized the signal-to-noise ratio of the Doppler measurements. Consequently, only relative $V_{max}$ was determined. However, changes in relative $V_{max}$ over time still could be measured accurately using this method because the eye could not move. The Doppler signal was recorded on magnetic tape and subsequently analyzed to determine relative $V_{max}$, using the method previously described.

Red-free fundus photographs were taken with a Topcon (Tokyo, Japan) TRC-W fundus camera in six cats, from which the diameter, $D$, of the erythrocyte column was determined. Relative blood flow in the retinal arterioles, $Q$, was obtained at baseline and at minimum BP after the drug was injected, using the relationship:

$$Q \propto D^2 \cdot V_{max}$$

**Relative ONH Blood Flow**

In 13 cats, the laser beam was focused at the ONH disc at a site away from visible blood vessels. The diameter of the optical fiber aperture used to detect the scattered light was 150 μm at the disc. This aperture was placed approximately 100 μm off the site directly illuminated by the laser beam. The photocurrent generated by the scattered light was analyzed with a TSI BPM 403A blood perfusion monitor (Vasamedics, Inc., St. Paul, MN) that was adapted to process the low light level signals from the ONH. When the laser beam is focused on a tissue, this instrument provides relative velocity, volume, and flux ($F = velocity \times volume$) of the erythrocytes in the illuminated volume of the tissue. In eight cats, we simultaneously recorded $F$ and relative blood velocity. From these two recordings, we calculated the corresponding changes in blood volume.

**Partial Pressure of Oxygen in ONH Tissue**

In one cat, an oxygen-sensitive single-barreled microelectrode (tip diameter, 4–7 μm; diameter-recess ratio, 1:10) was placed in the vitreous in front of the ONH disc. Our $P_{O2}$ measurement technique was described elsewhere. The microelectrode current ($\propto P_{O2}$) was recorded, together with BP and $F$. Before and after the injection of 20 μg/kg of nicardipine, we measured $F$ using a laser Doppler flowmeter based on a surgical microscope equipped with a diode laser at 812 nm.

Bolus doses of 20 and 100 μg/kg of nicardipine hydrochloride were injected intravenously. In the cats that received both doses, the smaller one was given first, and the larger one was administered after the BP had returned to preinjection levels (< 20 min later). The Doppler photocurrent from retinal vessels and $F$ were recorded continuously, starting a few minutes before the injection and ending when the BP returned to its preinjection level.

Paired student t-tests and Wilcoxon signed-rank tests were applied to evaluate the statistical signifi-

| Table 1. Baseline mean blood pressure, BP, heart rate, HR, arterial pH, $P_{CO2}$, and $P_{O2}$ |
|---------------------------------|-----------------|-----------------|
| BP (mm Hg)                     | 93 ± 6          |         |
| HR (min⁻¹)                     | 160 ± 8         |         |
| pH                             | 7.34 ± 0.03     |         |
| $P_{CO2}$ (mm Hg)              | 30 ± 3          |         |
| $P_{O2}$ (mm Hg)               | 101 ± 7         |         |

Mean ± 95% confidence limits; 27 cats.
Fig. 2. Representative recordings of $V_{\text{max}}$ (arbitrary units) in a retinal artery at baseline (preinjection) and various times after the intravenous injection of 20 $\mu$g/kg (A) and 100 $\mu$g/kg (B) of nicardipine. The mean blood pressure (BP) is shown at the bottom of each figure. The large and rapid variations of $V_{\text{max}}$ were synchronous with the cardiac cycle.

Table 1 shows the mean value of the vital systemic variables before the injection (baseline) of the drug in the 27 cats used in this study. Figure 1 displays representative time courses of the BP after the injection of 20 and 100 $\mu$g/kg of the drug in the same animal. Group average BP reached a minimum at 60 ± 27 sec after the injection. There was no significant difference in the magnitude of the maximum relative decrease in BP between the 20 and 100 $\mu$g/kg doses. In all 27 animals that received the 20-$\mu$g/kg dose and in 2 of the 8 cats that received the 100-$\mu$g/kg dose, the BP returned to baseline levels within approximately 10 min.

Representative recordings of relative $V_{\text{max}}$ during the heart cycle before the injection (baseline) and at 90 sec, 210 sec, and 10 min after injection of 20 $\mu$g/kg of nicardipine are shown in Figure 2A. Figure 2B shows such recordings at baseline, 37 sec, 90 sec, and 300 sec after injection of 100 $\mu$g/kg of nicardipine.

The results are presented as mean ± 95% confidence limits. Significance levels of $P < 0.05$ were considered statistically significant.

Results

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The group mean pulsatility of $V_{\text{max}}$ during the heart cycle, defined as $(V_{\text{max,s}} - V_{\text{max,d}})/(V_{\text{max,s}} + V_{\text{max,d}})$, was significantly larger at minimum BP (0.48 ± 0.18) than at baseline (0.34 ± 0.18, $p < 0.05$). This was a result of the significant decrease in relative $V_{\text{max}}$ during diastole for both doses. At minimum BP, the mean relative $V_{\text{max}}$ was significantly ($P < 0.02$) below baseline value (Table 2), both for the 20- and 100-μg/kg doses. Mean relative Q was not significantly different from baseline value after the 20-μg/kg dose, but it was significantly lower ($P < 0.05$) after the 100-μg/kg dose. With both doses, when the average BP had returned to baseline (89 ± 8 mmHg versus 93 ± 6 mmHg), mean relative $V_{\text{max}}$ and mean relative Q were not significantly different from baseline.

A typical time course of ONH F over 10 min after the injection of 20 μg/kg (11 cats) of nicardipine is shown in Figure 3. With a 20-μg/kg dose, 10 of 11 cats had a significant increase in F at 10 and 20 min ($P < 0.05$). In one cat, F decreased after injection of the drug and remained approximately 30% below normal for the duration of the measurements. The group mean increase in F, when the value of F was averaged in the interval of time between 7 and 10 min after the injection, was 19 ± 18% (Fig. 4). At 20 min after injection, it was 27 ± 24%. In the four cats that received the 100-μg/kg dose, this value was 30 ± 14% at 10 min.

From the simultaneous recordings of F and velocity changes after drug administration, we calculated that, when the increase in F was maximum, 75 ± 21% of this increase was a result of an increase in blood volume; the other 25% was caused by an increase in blood velocity. Simultaneous recordings of BP, F, and vitreous Po2 measured at the front of the disc are displayed in Figure 5. Parallel changes in F and Po2 were induced by the drug.

Table 2. Percentage changes (mean ± 95% confidence limits) of mean arterial blood pressure, BP, retinal artery diameter, D, maximum red blood cell velocity, $V_{\text{max}}$, and blood flow, Q, between preinjection values and values at minimum BP after drug injection

<table>
<thead>
<tr>
<th>Measured parameters</th>
<th>20 μg/kg (6 cats)</th>
<th>100 μg/kg (4 cats)</th>
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<tbody>
<tr>
<td>BP</td>
<td>$-23 \pm 9^*$</td>
<td>$-28 \pm 19^*$</td>
</tr>
<tr>
<td>D</td>
<td>$7 \pm 6^*$</td>
<td>$3 \pm 6$</td>
</tr>
<tr>
<td>$V_{\text{max}}$</td>
<td>$-17 \pm 11^+$</td>
<td>$-31 \pm 26^+$</td>
</tr>
<tr>
<td>Q</td>
<td>$-4 \pm 11$</td>
<td>$-26 \pm 20^*$</td>
</tr>
</tbody>
</table>

* $P < 0.05$.
† $P < 0.02$, W (Wilcoxon test) < 0.05.
‡ $P < 0.01$.

Fig. 3. Typical time course of optic nerve head F-change induced by the intravenous injection of 20 μg/kg. The top trace represents the time course of the mean arterial blood pressure.

Discussion

Our study found that nicardipine injected intravenously at doses of 20 and 100 μg/kg caused blood flow to increase in the ONH, even in the presence of a drop in arterial BP. By contrast, retinal blood flow, although unaffected by the smaller dose of the drug, decreased transiently with the larger dose. An increase in ONH blood flow occurred in all but one cat. We cannot explain the decrease observed in this cat; we may not have detected a possible motion of the incident laser beam caused by the large drop in arterial BP (50 mmHg) to a site of the disc that had a lower F. The magnitude of the increase in ONH F after injection of nicardipine was comparable to the flow increase observed in the dog brain (11%) and in human patients with ischemic diseases of the brain (17%), although the amount of drug administered in those studies was only 10 μg/kg.

At a dose of 20 μg/kg, retinal blood flow was not different from baseline (preinjection level) when the arterial BP was still lower than at baseline; this finding agreed with the property of the retinal circulation to autoregulate over a wide range of perfusion pressures. With the larger drug dose, retinal blood velocity decreased during the initial drop of BP because, we believe, the rate of decrease in BP was too fast for the autoregulatory system to counteract the drop in pressure. We do not think this was a direct effect of the drug on the vasculature. Previous measurements have shown that the time constant of the autoregulatory process is between 1–2 min.

The drug-induced increase in arterial blood velocity pulsatility could be a result of an increase in arterial wall compliance and a decrease in the characteristic arterial impedance at the level of the larger arteries, a finding that was observed in studies of the effect of nicardipine on blood flow in the forearm.
The difference in the responses between the retinal and ONH circulations was remarkable. Because this drug presumably acts on the outer wall of the vessels, the failure of retinal blood flow to increase may be related to the inability of the drug to cross the wall of the retinal vessels. However, in the ONH, diffusion of the drug from the choroidal circulation into the ONH tissue would allow the drug to reach the outer wall of the vessels. Another possibility is that the Doppler signal from the ONH predominantly originated from regions beyond the superficial ONH vascular layer of retinal origin and that the vasculature in these regions of choroidal origin responded to the drug in a manner similar to that of the brain vasculature.

The preliminary results from the simultaneous measurements of ONH blood flow and Po2 showed parallel increases in both parameters in accordance with previous findings obtained from the rat cortex, after the injection of nimodipine, also a calcium-channel blocker. These results also suggest that the drug does not affect oxygen consumption by ONH tissue. However, changes in ONH blood flow predominantly are caused by changes in blood volume, and this may be another explanation for the change in Po2, namely that the increase in blood volume brings the disc tissue closer to the microelectrode tip, resulting in an apparent increase in tissue Po2. Vitreal Po2 profiles in front of the disc must be obtained to confirm that the observed Po2 increase represented a real tissue Po2 change.

The increases in blood volume represent increases in blood vessel capacitance that occur either through increases in the caliber of the venules or recruitment...
of capillaries.\textsuperscript{19,20} It is not possible currently, however, to define the process better by which the blood volume is increased by this drug.

The efficient autoregulatory capability of the ONH was evident from the rapid return of \( F \) to baseline value after the abrupt decrease in BP shortly after injection (Figs. 3, 5). A similarly efficient autoregulation was demonstrated in recent measurements of \( F \) after step increases in intraocular pressure in cats.\textsuperscript{21} The small initial decrease in \( F \), in phase with the decrease in systemic BP observed in some animals (Figs. 3, 5), probably was a result of the drop in BP occurring too quickly for the autoregulation process to be fully operational.

A central difficult question in the application of laser Doppler flowmetry to tissue blood flow is the depth of the sampled volume. In the ONH, depending on this depth, different vascular beds may contribute to the Doppler signal. This question was discussed theoretically in a previous article.\textsuperscript{11} Our analysis and an experimental study of the effect of optic nerve tissue slices of varying thickness on the laser Doppler signal\textsuperscript{22} strongly suggested a contribution from the lamina cribrosa to the Doppler signal from the ONH in addition to that from the anterior ONH vasculature and lamina choroidalis. Furthermore, the results of our current study, demonstrating that nicardipine significantly increases ONH \( F \) but not retinal blood flow, provided additional evidence that the sampled volume included layers of the ONH deeper than those supplied by retinal vessels.

In conclusion, we suggest there is no direct effect of an intravenous injection of up to 100 \( \mu \)g/kg of nicardipine on the retinal circulation of the cat during the first 10 min after injection because the decrease in blood flow can be explained by the drug-induced drop in arterial BP. Nicardipine produces, however, a significant increase in ONH blood flow despite a drop in systemic BP. Our study found, for the first time to our knowledge, a drug-induced increase in ONH blood flow that could have a beneficial effect on ONH tissue.

Key words: nicardipine, laser Doppler velocimetry–flowmetry, retinal–optic nerve circulation, blood flow, autoregulation, \( \text{PO}_2 \).

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References