Cerebrovascular autoregulation is resistant to calcium channel blockade with nimodipine

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Summary. In normal baboons cerebrovascular resistance changed along with blood pressure to maintain blood flow constant. This 'autoregulation' was not significantly altered in animals treated with a dose of the calcium channel blocker nimodipine causing selective cerebral vasodilation.

Key words. Baboon; ^{133}xenon; cerebral blood flow; cerebrovascular resistance; autoregulation; nimodipine; calcium.

Despite much debate over the physiological mechanisms behind autoregulation, it is clear that cerebral blood flow (CBF) is relatively independent of alterations in systemic perfusion pressure. When mean arterial blood pressure (MBP) is raised from the normotensive value of approximately 100 mm Hg, to a pressure of 140 mm Hg, a cerebral vasoconstriction occurs to maintain CBF relatively constant. Also, when MBP is reduced from 100 to 60 mm Hg a cerebral vasodilation occurs to similarly maintain CBF[1,2]. Other mechanisms operate to modulate CBF and tightly regulate flow to metabolism. We have previously shown that in many of these instances the cerebrovascular response is dependent on the presence of extracellular calcium[3]. This dependence on extracellular calcium provides a basis for the relatively selective vasodilating effect of calcium channel blocking drugs on cerebral arteries when compared to general systemic arteries[4,5]. However, further in vitro evidence suggests that the cerebrovascular contractile response to a stretch does not fall into this pattern and is resistant to blockade with the calcium blocking drugs[4,6,7]. If this myogenic response correlates to the in vivo autoregulatory adjustments, then the cerebrovascular responses to alteration in MBP should be relatively intact after calcium channel blockade in vivo. The present study was to determine the status of CBF autoregulation during infusion of the calcium channel blocker, nimodipine (NIM), at a dose which was previously shown to be effective in improving CBF and inhibiting CBF responses to other agonists[8].

Adult baboons (*Papio cynocephalus*, 10–15 kg) were sedated with intramuscular ketamine (Ketalar, 5 mg/kg) and anesthetized with sodium pentobarbital (Nembutal, 30 mg/kg, i.v.). The animals were intubated and ventilated with 70% N_2O in O_2. This N_2O with supplemental barbiturate when required was used to maintain anesthesia with the EEG at a dominant alpha rhythm (8–10 Hz). The depth and rate of ventilation were set at values to maintain arterial normocapnia (PCO_2 = 40 mm Hg) and normoxia (PO_2 = 100 mm Hg). These values were checked frequently throughout the experiment. A femoral arterial catheter was used to monitor mean arterial blood pressure (MBP). Finally, CBF was measured using the ^{133}xenon clearance technique previously described[8]. Briefly, the arrival into and clearance from the brain of a bolus intracarotid injection of ^{133}xenon was monitored using an external gamma counting sodium iodide crystal. CBF was calculated from the clearance curve using the height-over-area technique previously described[8]. The ratio of MBP to CBF was used to calculate cerebrovascular resistance (CVR).

We studied the ability of the baboons to regulate CBF when MBP was first decreased by removal of blood volume from the venous catheter and then when MBP was increased by intravenous reinfusion of the autologous blood. The measurements were always made during stable control conditions of EEG and blood gases. Three control animals were studied. In a second group of 4 baboons the baseline measurements were followed with intravenous infusion of NIM at 1 μg/kg/min. The measurements were repeated after 15 min of the NIM infusion. Then the ability of these NIM-treated animals to regulate CBF during similar manipulation of blood volume and MBP was determined.

Alterations within control or NIM-treated groups were statistically compared (Stats-2 software, Statsoft, Tulsa) using an analysis of variance with repeated measures. Difference between baseline and blood withdrawal/infusion groups were tested using a paired Wilcoxon non-parametric test. Significance was accepted at the 5% level of probability. In the normal animals (table, top) MBP was reduced from 112+/−6 to 84+/−5 mm Hg by withdrawal of blood volume. There was no significant alteration in CBF, while CVR showed a decrease (2.49+/−0.28 and 1.89+/−0.11 mm Hg/ml · min^{-1} per 100 g). Reinfusion of the blood increased MBP back to 118+/−6 mm Hg with no alteration in CBF and an increase in CVR to 2.57+/−0.20 mm Hg/ml · min^{-1} per 100 g. Analysis of variance showed that a significant alteration of CVR had occurred and the paired Wilcoxon test showed that the values after withdrawal of the blood were lower than baseline ($p < 0.05$). Thus, when MBP was decreased the controls showed a decreased CVR of 0.22+/−0.04 mm Hg/ml · min^{-1} per 100 g for each 10 mm Hg that MBP was lowered. Similarly, when MBP was increased the controls showed an increased CVR of 0.20+/−0.03 mm Hg/ml · min^{-1} per 100 g for each 10 mm Hg that MBP was raised.

Cerebrovascular and systemic measurements. The table shows the mean (+/− one standard error) of the mean arterial blood pressure (MBP), the arterial PCO_2, the arterial PO_2, and the cerebral blood flow (CBF) during baseline, hypovolemic and hypervolemic conditions.

	MBP (mm Hg)	PCO_2 (mm Hg)	PO_2 (mm Hg)	CBF (ml/min/100 g)
Normal controls (n = 3)				
Baseline	112.0 +/−5.6	38.9 +/−0.1	112.3 +/−16.6	45.8 +/−3.0
Blood loss	83.7 +/−4.9	38.2 +/−0.7	103.6 +/−6.7	44.6 +/−3.7
Reinfusion	118.3 +/−6.2	39.5 +/−0.3	104.9 +/−8.8	46.3 +/−2.1
Nimodipine (n = 4)				
Baseline	118.6 +/−4.9	39.3 +/−0.3	101.5 +/−5.0	45.4 +/−0.9
NIM 1 μg/kg/min	105.7 +/−4.5	39.6 +/−1.8	119.4 +/−8.7	57.4 +/−2.7
NIM + Blood loss	84.0 +/−4.5	40.6 +/−1.6	119.8 +/−15.5	57.7 +/−2.2
NIM + Reinfusion	106.2 +/−5.3	40.1 +/−1.3	128.8 +/−23.1	57.6 +/−5.6

NIM at 1 μg/kg/min increased CBF (table, bottom, $p < 0.05$, paired Wilcoxon, $n = 4$). This increased CBF was not accompanied by significant alteration in MBP, or arterial blood gases, and thus was due to a decrease in CVR from $2.62 +/- 0.16$ to $1.79 +/- 0.08$ mm Hg/ml · min^{-1} per 100 g. With continued NIM infusion blood was withdrawn to reduce MBP from $106 +/- 4$ to $84 +/- 4$ mm Hg. CBF was not significantly altered by this drop in MBP while CVR showed a decrease to $1.46 +/- 0.09$ mm Hg/ml · min^{-1} per 100 g. Finally, when the blood was reinfused to raise the MBP again to 107 mm Hg, the CBF again showed no significant alteration and the calculated CVR was significantly increased to $1.90 +/- 0.22$ mm Hg/ml · min^{-1} per 100 g. Similar analysis of variance and Wilcoxon tests showed that in these NIM treated animals when MBP was reduced the CVR decreased by $0.23 +/- 0.07$ mm Hg/ml · min^{-1} per 100 g for each 10 mm Hg drop in MBP. Similarly an increased MBP by 10 mm Hg caused an increased CVR of $0.16 +/- 0.06$ mm Hg/ml · min^{-1} per 100 g. No significant alteration in arterial PCO_2 or PO_2 was found in any of the control or NIM experiments (table). In addition all animals displayed an EEG rhythm of 8–10 Hz throughout each experiment.

The present experiments confirm that infusion of NIM at the low dose of 1 μg/kg/min causes modest increase in CBF without significant alteration in MBP. The percentage improvement in CBF compares well with other similar studies[8,9], and the vasodilation may be attributed to NIM antagonism of some portion of vasomotor tone. The present study (and that of Harris et al.[10]) suggests that the autoregulatory CBF responses to moderate changes in MBP are not part of that NIM sensitive tone. By contrast, our previous study[8] and a similar study in the rat[11] showed that higher doses of NIM caused CBF and MBP to be reduced together, suggesting a loss of autoregulation at high doses. Other studies indicate that even low doses of NIM can inhibit the autoregulatory adjustment to altered MBP[12–14]. However, all these experiments were investigations of a much larger MBP stimulus, potentially recruiting additional (or different) vasoactive mechanisms than the modest stimulus in our present study. The present results, however, may be more applicable to the situation in a NIM-treated individual where CBF remains protected against the relatively small MBP changes associated with everyday life.

In support of our present in vivo observations, are a number of in vitro studies showing that cerebral vessels will contract when stretched and that this response is resistant to calcium channel blocking drugs[6,7]. If in vivo the autoregulatory response to increased MBP is a result of these myogenic contractions, then it might be predicted that in vivo autoregulation would be resistant to small doses of NIM. Our results provide indirect evidence that in vivo autoregulation correlates with in vitro vascular myogenic responses, and may be interpreted as evidence that in vivo autoregulation is dependent on a vascular smooth muscle myogenic response. This projection is further supported by the previous observations that the CBF dilator response to altered PCO_2 (a metabolite) is potently blocked by NIM treatment[8,10,12].

In summary, the present study shows that in vivo CBF autoregulation to altered MBP is intact with low dose calcium channel blockade using NIM. Thus the pharmacological increase in CBF with the drug is not at the expense of this important control mechanism. Finally, these studies suggest that in vivo autoregulation is more closely correlated with myogenic contraction of vascular smooth muscle than with CBF sensitivity to a major metabolite, CO_2.

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