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The Influence of Indomethacin on the Autoregulatory Ability of the Cerebral Vascular Bed in the Newborn Lamb

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ABSTRACT. Prevention of hyperperfusion of the brain in the perinatal period has been thought to be an important mechanism by which indomethacin reduces the risk for severe periventricular-intraventricular hemorrhage. The present study investigated whether an indomethacin-induced enhancement of the upper limit of cerebral vascular autoregulatory ability in the neonate contributed to this reduction in cerebral blood flow. In seven anesthetized newborn lambs, we measured temporal blood flow velocity (TMFV) in the carotid artery over a wide range of mean aortic blood pressures (MABP) before and 30 min after an i.v. dose of 1 mg/kg indomethacin. TMFV in the carotid artery was used as an estimate for changes in cerebral blood flow. Stepwise changes in MABP of approximately 10 mm Hg were achieved by progressive balloon occlusion of the thoracic aorta or by progressive bleeding. Multiple linear regression analysis of TMFV *versus* MABP, indomethacin, and the possible interactive effects confirmed that, at MABP values up to 86 mm Hg, indomethacin lowered TMFV of the carotid artery. Above 86 mm Hg, indomethacin reduced the slope of the TMFV-MABP relationship, indicating an improvement of the autoregulatory ability of the cerebral vascular bed. There was a significant interanimal variability. Thus, indomethacin may reduce the risk for PIVH by limiting cerebral blood flow, especially during increased cerebral perfusion pressures, which often occur after birth asphyxia. (*Pediatr Res* 34: 178–181, 1993)

Abbreviations

MABP, mean aortic blood pressure
PIVH, periventricular-intraventricular hemorrhage
TMFV, temporal mean flow velocity

Neonatal PIVH causes significant mortality and morbidity (1, 2). Birth asphyxia with subsequent prostaglandin-induced postasphytic hyperperfusion of the neonatal brain may be an important cause of PIVH (3, 4) and has generated interest in pharmacologic prevention studies. Indomethacin, a cyclooxygenase inhibitor, has been found to decrease the risk for PIVH when given within 12 h after birth (5–9). Indomethacin is thought to act by attenuating brain blood flow and by modulating the vasodilatory effect of hypercapnia on cerebral resistance vessels (10, 11). Recent reports (12, 13) also suggest that cyclooxygenase inhibitors enhance the autoregulatory ability of the neonatal cerebral vascular bed, which also may contribute to the decrease in the occurrence of PIVH.

We therefore investigated the influence of indomethacin on cerebral blood flow and especially on the upper limit of the autoregulatory ability of the cerebral vascular bed in the newborn lamb.

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MATERIAL AND METHODS

Animal preparation. Surgical and experimental procedures used were reviewed and approved by the Committee on Animal Experiments at the University of Leiden and the scientific board of the Department of Pediatrics.

Ten newborn lambs with weights ranging from 3.5 to 5.9 kg (mean ± SD; 4.7 ± 0.7 kg) and ages ranging from 2 to 11 d (mean ± SD; 5.6 ± 3.0 d) were studied. Nine out of 10 animals were studied in the first wk of life. After premedication with ketamine hydrochloride (3 mg/kg i.v.), general anesthesia was maintained using continuous infusion of ketamine hydrochloride (8–30 mg/kg/h), adjusted according to heart rate and blood pressure changes in response to external stimuli. After intubation, the lambs were ventilated with oxygen and air using a pressure-regulated ventilator that was adjusted to maintain arterial P_{O_2} and P_{CO_2} in the normal range. Pancuronium (0.2 mg/kg i.v.) was administered for muscle relaxation. An i.v. infusion of 10% dextrose in 0.5 N NaCl solution was maintained throughout the study at about 4 mL/kg/h. $NaHCO_3$ was supplemented if the arterial pH was lower than 7.26.

Estimation of cerebral blood flow. The left carotid artery was insonated to obtain its Doppler-derived velocity wave form. After exposing the carotid artery in the neck, an appropriately sized 20-MHz Doppler flow probe was applied to fit around the vessel and connected to a range-gated pulsed Doppler flow meter (Crystal Biotech, Holliston, MA). The range-gate was adjusted to detect the highest possible velocity for subsequent determination of the optimal blood flow velocity wave form. TMFV of the carotid artery, expressed in cm/s, was used to estimate changes in actual cerebral blood flow (14).

Changes in cerebral perfusion pressure. In the right and left femoral arteries and veins, 6F or 7F self-sealing sheaths were placed using a percutaneous technique. In one femoral artery, a 5F atrioseptostomy catheter (American Edwards Laboratories, Irvine, CA) was advanced to the midthoracic aorta. In the other femoral artery, a 5F micromanometer catheter (Millar Instruments, Houston, TX) was advanced into the thoracic aorta and situated proximal to the balloon catheter for measurement of instantaneous mean aortic pressure. Both femoral venous catheters were used for blood withdrawal and reperfusion and for

administrating drugs. Cerebral perfusion pressure was increased by stepwise balloon occlusion of the aorta and decreased by stepwise bleeding (via a femoral vein).

Physiologic measurements. Arterial blood gases and pH were measured using a Corning 178 pH/blood gas analyzer (Corning, Halstead, UK). Blood gases, pH, and hematocrit were determined at regular intervals and adjusted as necessary.

Study protocol. After completion of the surgical preparation, a 30-min period was allowed to achieve hemodynamic stability. During the control condition, MABP was increased in steps of approximately 10 mm Hg by stepwise balloon occlusion, starting from baseline (baseline level I). After each step and during steady state, TMFV of the carotid artery was determined from the velocity wave form during 20 to 30 consecutive heart beats. After maximal aortic occlusion, the aortic balloon was released (baseline level II). Then, stepwise bleeding was executed in an attempt to lower MABP to a value near the assumed lower limit (40 to 45 mm Hg) of cerebral autoregulation (15, 16). Because we were especially interested in the action of indomethacin on the upper limit of cerebral autoregulation and because too-low perfusion pressures could disturb cerebral autoregulatory ability, we never decreased mean aortic pressure below 42 mm Hg. The blood was carefully reperfused afterwards, and after stabilization of the MABP, 1 mg/kg indomethacin was administered i.v. over 1 min. After 30 min or after reaching hemodynamic stability, the procedure followed during the control condition was repeated (postindomethacin condition).

MABP as well as the blood flow velocity wave form of the carotid artery were continuously displayed on a memory oscilloscope (Gould OS 4100, Hainault, UK). The blood flow velocity wave form of the carotid artery, ECG, and aortic pressure were digitized with a sample frequency of 200 Hz and stored on hard disk using a personal computer.

Statistical analysis. If cerebral autoregulation is present, the relationship between cerebral perfusion pressure and cerebral blood flow is expected to be nonlinear over the full range of perfusion pressures, but fairly linear below the lower limit, between the lower and upper limits, and above the upper limit of the autoregulatory range. As we were interested in the upper-limit range of the autoregulation, we defined two ranges of MABP in which we investigated the relation between TMFV and MABP separately, using a linear regression model: *1*) Between MABP values of about 45 mm Hg and the upper limit of cerebral autoregulation, and *2*) at MABP values above this upper limit. In the control condition, the upper limit breakpoint of the autoregulatory plateau was determined mathematically by repetitively fitting a linear regression model through the data (TMFV-MABP relationship) above and below a test point using different test points in the range from 75 to 95 mm Hg. To correct for interanimal variability, we included dummy variables to code the different animals (see below). The breakpoint was defined as the test point where the sum of the residuals from the two fits was minimal (16, 17).

To investigate whether indomethacin had a significant effect on the autoregulatory ability of the cerebral vascular bed of the newborn lamb, we analyzed the TMFV-MABP relationship with and without indomethacin over the two above-defined pressure ranges. We used a multiple linear regression model with dummy variables in both above-defined ranges, and the following regression equation:

$$Y = b_o + b_M MABP + b_I I + b_{M\cdot I} MABP \cdot I + \sum_{k=1}^{6} b_{l_k} L_k$$

where Y is the dependent variable (TMFV), and b_o is its overall mean value over all conditions and all animals. MABP is the first independent variable, and its coefficient b_M defines the slope of the pressure-flow relationship, which is used as indicator of autoregulatory ability. If this parameter is not significant, there is strong autoregulation, because flow does not depend on perfusion pressure. There is one drug (dummy) variable, I, representing the control condition (value 0) or the postindomethacin condition (value 1). The coefficient b_i indicates the independent effect of indomethacin on TMFV, thus affecting the intercept of the TMFV-MABP relationship. The third independent variable is an interaction variable, MABP·I, representing the interactive effect of indomethacin and MABP on the TMFV. The coefficient $b_{M\cdot I}$ indicates, therefore, the effect of indomethacin on the slope of the TMFV-MABP relationship. Finally, to correct for interanimal variability, six dummy variables (L_1–L_6) were introduced for the seven animals included in this analysis (18). To determine the statistical significance of any variable, an F test was performed by dividing the mean square of that variable by the mean square residual.

Differences in pH, P_{CO_2} and P_{O_2}, MABP, and hematocrit among the four baseline values (baseline I and II during the control condition, baseline I and II during the postindomethacin condition) were investigated by analysis of variance for repeated measurements followed by the Newman-Keuls test if statistically significant differences were obtained. Statistical significance was assumed for $p < 0.05$. Groups of data are summarized as mean ± 1 SD.

RESULTS

Each measurement was performed after steady state had been reached, which, on the average, took 3 to 5 min after every change in aortic pressure. We sampled the TMFV-wave form and aortic pressure for 40 s and used representative recordings for further analysis. In seven of the 10 animals, we were able to obtain a sufficiently large range of MABP-values from near the presumed lower limit of 40 to 45 mm Hg to well above the calculated upper limit (see below) of cerebral autoregulation in newborn lambs. Only the results obtained from these seven lambs were used for statistical evaluation as described in this section. Immediately after indomethacin administration, there was a sharp rise of MABP in all cases, but in all animals, MABP decreased within 30 min to values not significantly different from those measured during the baseline conditions before indomethacin. Also, no differences were found between baseline values of other pertinent clinical variables in any baseline condition (Table 1).

Figure 1 shows the plot of all individual values of TMFV against MABP. The calculated upper limit of the autoregulatory ability of the cerebral vascular bed of the newborn lamb appeared to be 86 mm Hg, which was in accordance with data in literature (15, 16). The test points used to arrive at this value ranged from 75 to 95 mm Hg.

The values of MABP in which cerebral autoregulation was supposed to be operative, ranged from 42 to 86 mm Hg (upper limit indicated by arrow in Fig. 1). Using the multiple linear regression model, we found a small but significant effect of MABP on TMFV (b_M: 0.23 cm·s^{-1}/mm Hg) in this range and a slope whose value was not significantly affected by indomethacin ($b_{M\cdot I}$: NS). In contrast, indomethacin did affect the intercept of the relationship significantly (from 15.85 to 1.04 cm·s^{-1}), indicating that indomethacin had a pressure-independent effect on flow (b_I: −14.8 cm·s^{-1}), decreasing it for any given pressure over the autoregulatory range. The results are summarized in Table

Table 1. *Clinical data (means ± 1 SD) at baseline levels I and II before and after indomethacin administration of seven newborn lambs*

	Before indomethacin		After indomethacin	
	Baseline I	Baseline II	Baseline I	Baseline II
pH	7.35 ± 0.05	7.38 ± 0.07	7.34 ± 0.04	7.34 ± 0.07
P_{CO_2} (kPa)	4.6 ± 0.8	4.5 ± 0.9	5.1 ± 1.0	5.0 ± 0.7
P_{O_2} (kPa)	13.3 ± 3.4	12.1 ± 1.9	12.7 ± 4.2	11.1 ± 3.9
MABP (mm Hg)	65 ± 7	63 ± 10	72 ± 13	69 ± 18
Hematocrit (L/L)	39 ± 2	41 ± 3	43 ± 2	41 ± 2

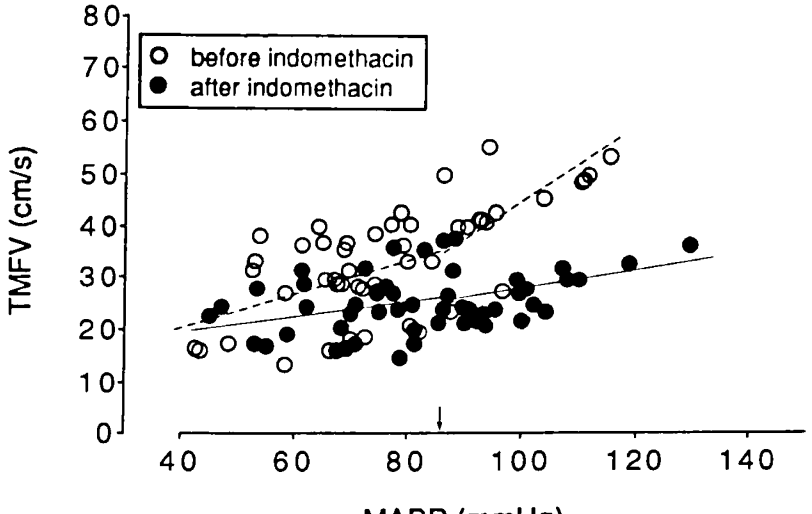

Fig. 1. Individual values of the TMFV as a function of MABP before and after indomethacin administration. The lines represent the regression lines of the TMFV-MABP relationship before (- - -) and after (—) indomethacin administration over the pressure ranges below and above the highest MABP value (86 mm Hg; *arrow*) at which cerebral autoregulation is supposed to be operative, respectively. For explanation about how this point was determined, see text.

Table 2. *Results of multiple linear regression analysis of TMFV (dependent variable) on two independent variables: MABP (b_M) and drug variable I (whose coefficient b_I indicates independent effect of indomethacin on TMFV), and interaction variable MABP·I (whose coefficient $b_{M\cdot I}$ indicates interactive effect of indomethacin on slope of TMFV-MABP relationship***

	b_o	b_M	b_I	$b_{M\cdot I}$	L1	L2	L3	L4	L5	L6
MABP < 87 mm Hg										
b	15.85	0.23	−14.81	0.09	5.73	5.54	−10.93	−8.95	−0.48	−2.04
SEM	4.09	0.04	3.18	0.05	1.21	1.44	1.42	1.20	1.10	1.19
p		<0.0001	<0.05	NS			<0.0001			
MABP > 86 mm Hg										
b	−6.61	0.37	8.02	−0.23	5.74	1.24	−9.66	−6.55	−0.48	−2.04
SEM	10.54	0.08	8.99	0.09	2.26	1.29	1.45	2.08	0.95	0.94
p		<0.0001	NS	<0.05			<0.001			

* b_o is the overall intercept. For correction of interanimal variability, six dummy variables for seven animals were introduced (L1–L6). This analysis was done for two ranges of pressure (MABP < 87 mm Hg and MABP > 86 mm Hg). Their regression equations were statistically significant ($p < 0.0001$ and $p < 0.0001$, respectively).

2. Above 86 mm Hg (Table 2), MABP had a larger effect on TMFV during the control condition (b_M: 0.53 cm·s^{-1}/mm Hg). However, in this range, indomethacin did have a significant effect on the slope of the pressure-flow relationship ($b_{M\cdot I}$: −0.23 cm·s^{-1}/mm Hg). This means that indomethacin reduced the slope of the TMFV-MABP relationship significantly from 0.37 to 0.14 cm·s^{-1}/mm Hg. This reduction in slope is a reflection of an improvement of the autoregulatory ability: the autoregulatory range appears to be greatly expanded, as shown in Figure 1. Indomethacin had no significant pressure-independent-lowering effect on TMFV above 86 mm Hg. It is also clear from Table 2 that there is a significant interanimal variability in both investigated MABP ranges, which reflects the biologic variance.

After completion of the study, balloon catheter positions were checked. Moreover, in all animals, the ductus arteriosus appeared to be closed.

DISCUSSION

The present study shows that indomethacin decreases TMFV of the carotid artery and reduces the slope of the TMFV-MABP relationship at higher levels of MABP as compared with the control condition. Although reductions in TMFV may indicate reductions in actual cerebral blood flow, the simultaneous changes in blood pressure may induce autoregulatory alterations in the diameter of the vessel under investigation (*i.e.* the carotid artery), which will result in changes of the velocity wave form without changes in actual cerebral blood flow. Although the diameter of the carotid artery may change to some extent during changes in blood pressure, cerebral vascular resistance (if cerebral autoregulation is intact) will largely be controlled by the cerebral arterioles situated distal to the carotid arteries, whose diameters remain relatively unchanged (14, 19, 20). We used the TMFV of the extracranially situated (common) carotid artery, which supplies the brain with only 50 to 70% of its total blood flow. However, an earlier study in newborn lambs has reported a close correlation between the extracranially measured carotid artery TMFV, using electromagnetic flow probes, and the Doppler-derived TMFV from an intracranially situated major artery using an artificial fontanel (21). That indomethacin should disturb this relation because of disproportional constriction of extracranially situated branches of the carotid artery, supplying muscle and skin, is not likely. Studies investigating the effect of indomethacin on the muscular arterial vascular bed have reported only a modest effect of indomethacin on the arteries and arterioles of the muscles (22–24), contrary to the action of indomethacin on the resistance vessels in the brain. It is also not very likely that ketamine hydrochloride, used as anesthetic in our experiments, could have influenced the relation between TMFV of the carotid artery and true cerebral blood flow, because its cardiovascular effect is small and only transient (25). We therefore suggest that changes of the TMFV of the carotid artery can be used reliably as marker for changes in cerebral blood flow.

Several clinical studies have reported a decrease in the incidence of severe PIVH in the preterm baby after early indometh-

acin treatment. The present study suggests that this lower incidence of PIVH may, at least partially, be caused by reduction of cerebral hyperemia by indomethacin: the enhancement of the autoregulatory ability of the neonatal cerebral vascular bed at high cerebral perfusion pressures may confine the hyperemia associated with asphyxia and hypercarbia at birth. Earlier experimental and clinical studies have demonstrated a relationship between hyperperfusion of the neonatal brain (26) and impaired autoregulation of the neonatal cerebral vascular bed (27) on the one hand and the occurrence of PIVH on the other hand. Indomethacin may abolish this process or, at least, limit its deleterious consequences.

We did find a small but significant relationship between TMFV and MABP in the autoregulatory range of MABP. In an ideally autoregulated bed, such a relationship should be absent. Possible mechanisms for its occurrence include the acute effects of instrumentation and/or anesthesia, but this has not previously been demonstrated. Moreover, the animals were all in good condition during the experiments. An alternative explanation may be that some measurements were obtained below the autoregulatory range; when we excluded the measurements made at MABP values below 45 mm Hg, the relationship indeed disappeared. Lastly, the presence of the relationship may be caused by some involvement of the extracerebral vascular bed, which is not autoregulated.

As stated earlier, we did not collect data at MABP values well below the supposed lower limit of cerebral autoregulation (<40 mm Hg) to determine whether indomethacin might affect cerebral blood flow below the autoregulatory range (28). Thus, it remains to be investigated whether indomethacin has a negative effect on cerebral blood flow (and metabolism) at lower cerebral perfusion pressures. Furthermore, it remains to be determined whether or not the proven ability of indomethacin to act as a protector against oxygen-free radical injury of the vessels in the neonatal brain (29, 30) may also be instrumental in the decrease of severe PIVH: birth asphyxia-related excessive free-radical activity in combination with abnormalities in cerebral blood flow regulation have been implicated in the genesis of PIVH in the newborn animal model (31, 32).

In summary, the present study suggests that indomethacin decreases cerebral blood flow and enhances the autoregulatory ability of the cerebral vascular bed of the newborn lamb at increasing cerebral perfusion pressure. We speculate that the mechanism by which this drug reduces the risk for severe PIVH is by effectively preventing high cerebral blood flow values during periods of increased cerebral perfusion pressures. Such periods often occur during and immediately after birth asphyxia and/or during hypercarbia-induced vasodilation of the resistance vessels of the cerebral vascular bed. The effects of indomethacin on cerebral perfusion and autoregulation during cerebral perfusion pressures lower than 40 mm Hg were not investigated in this study and remain to be determined. A negative effect of indomethacin on cerebral blood flow and metabolism at lower perfusion pressures may possibly counteract its beneficial influence on autoregulatory ability of the cerebral vascular bed at high cerebral perfusion pressures.

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