Changes in Cerebrovascular Prostaglandins and Thromboxane as a Function of Systemic Blood Pressure

Cerebrovascular Flow Autoregulation of the Newborn

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Cerebrovascular concentrations of prostaglandin E (PGE), prostaglandin F\textsubscript{1α} (PGF\textsubscript{1α}), 6-ketoprostaglandin F\textsubscript{1α} (6-keto-PGF\textsubscript{1α}), and thromboxane B\textsubscript{2} (TXB\textsubscript{2}) were determined over a blood pressure range of 17–117 mm Hg (induced by inflation of balloon-tipped catheters placed in the thoracic descending aorta and at the aortic root) in eight newborn piglets to assess the role of prostanoids in cerebral blood flow (CBF; measured using radioactive microspheres) autoregulation. Basal systemic blood pressure, heart rate, blood gases, total CBF, and prostanoid concentrations were stable. CBF was constant between 50 and 90 mm Hg, but beyond this range CBF varied directly with blood pressure (τ=0.48; p<0.05). Sagittal sinus concentrations of PGE, PGF\textsubscript{2α}, and 6-keto-PGF\textsubscript{1α} varied with blood pressure according to a quadratic function (R\textsuperscript{2}=0.92 to 0.96; p<0.0001), exhibiting lowest values between mean blood pressures of 60 and 90 mm Hg. During hypotension (17–49 mm Hg), there was a greater relative increase in sagittal sinus concentrations of TXB\textsubscript{2} than of PGE, PGF\textsubscript{2α}, and 6-keto-PGF\textsubscript{1α}; at the lowest blood pressures, TXB\textsubscript{2} increased by 658±44%, and prostaglandins increased on the average by 331±49% (p<0.01) from their values during normotension (50–90 mm Hg). During hypertension (91–117 mm Hg), cerebrovascular production and concentrations of prostaglandins increased by 142±31% and 45±10%, respectively, but did not change for TXB\textsubscript{2}. Based on these findings we speculate that the marked increase in the potent vasoconstrictor thromboxane during hypotension may set the lower limit of CBF autoregulation to a blood pressure of 50 mm Hg and that the increase in vasodilator prostaglandins during hypertension may contribute to the pressure passivity of CBF above 90 mm Hg. These data may imply that the increase in cerebrovascular prostaglandins during relatively mild elevations in blood pressure may lead to distention and ultimately rupture of cerebral blood vessels in the newborn. (Circulation Research 1990;67:674–682)

The fetus and newborn exhibit autoregulation of cerebral blood flow (CBF) over a narrow range of systemic blood pressures.\textsuperscript{1,2} The mechanisms determining the limits of CBF autoregulation are not known. Prostaglandins affect CBF of the newborn\textsuperscript{3,4} and may be involved in the regulation of CBF at the lower limit of the CBF autoregulatory range.\textsuperscript{5,6} Brain and sagittal sinus concentrations of prostaglandins have been shown to increase during hypotension, possibly to maintain CBF.\textsuperscript{4,4} In addition, studies by Ment et al\textsuperscript{7} imply that prostaglandins may also play a role near the upper limit of CBF autoregulation, because indomethacin attenuated the increases in CBF during hypotension/volume reexpansion.

Prostanoid concentrations in the cerebral vasculature of the newborn have not been measured over a wide range of systemic blood pressures and beyond the limits of CBF autoregulation. We propose that, if prostanoids are involved in CBF autoregulation, their cerebrovascular concentrations will change as a function of systemic blood pressure. The information obtained from these changes in prostaglandin and thromboxane concentrations may help to define the contribution of prostanoids in setting the range of CBF autoregulation in the newborn. Therefore, we measured the major cerebrovascular prostaglandins\textsuperscript{8,9} and thromboxane B\textsubscript{2} (TXB\textsubscript{2}) over a wide range of systemic blood pressures and beyond the limits of CBF autoregulation, using the newborn piglet as a model. To relate changes in prostanoid concentrations as a function of blood pressure to CBF autoregulation, we...
also determined both the upper and lower limits of CBF autoregulation in the same animals.

Materials and Methods

This study was approved by the Animal Care and Ethics Committee of the McGill University-Montreal Children's Hospital Research Institute.

Surgical Preparation

Eight 1–3-day-old newborn piglets (1.2–1.6 kg) were studied. A diagram of the experimental preparation is shown in Figure 1. The piglets were anesthetized with halothane for catheterization of the blood vessels. A 3.5F polyethylene umbilical vessel catheter (Argyle, Sherwood, St. Louis) was placed into the left ventricle via the right subclavian artery for the injection of radiolabeled microspheres. The left subclavian artery was catheterized (3.5F, Argyle) for blood pressure recording and for withdrawal of blood samples including reference samples. A 5F silicone-coated balloon-tipped catheter fenestrated near its end (Angiocath, Berman, Arrow, Reading, Pa.) was placed in the ascending aorta immediately distal to the root of the aorta, via the right common carotid artery. In the piglet, ligation of one carotid artery does not modify CBF.3,6,10 By filling the balloon at the aortic root, hypotension was produced in the aortic arch, and its fenestrations enabled blood pressure to be continuously recorded in the aortic arch using a Statham pressure transducer (Glen Burnie, Md.) connected to a multichannel recorder (DR-8, Electronics for Medicine, White Plains, N.Y.). A second balloon-tipped catheter (4F Angiocath, Berman) was introduced into the thoracic descending aorta via a femoral artery. Filling of this balloon produced hypertension in the aortic arch. A small polyethylene catheter (Intramedic PE-50, Becton Dickinson, Parsippany, N.J.) was placed in the sagittal sinus via a small burr hole in the skull, for blood sampling. Electrocardiographic leads were placed on the skin to monitor the heart rate continuously.

After catheterization, the piglets were allowed to recover from anesthesia under an overhead lamp for 3–4 hours. For the purpose of experimentation, the awake piglets were placed under an infant radiant warmer to maintain their body temperature at 38°C, and they were fitted comfortably on a cloth sling that did not interfere with breathing movements. To avoid

Figure 1. Schematic representation of the surgical preparation and summary of the study design. BP, blood pressure; CBF, cerebral blood flow. (Refer to “Materials and Methods” for details.)
movement artifacts of our various measurements, the piglets' limbs were loosely restrained.

**Experimental Protocol**

A summary of the study design is found in Figure 1. The piglets were kept calm but awake by breathing spontaneously, into a sealed mask, a prepared gas mixture of 50% N₂O, 20% O₂, and 30% N₂, which does not affect CBF autoregulation. The baseline CBF was determined. Twenty minutes later one of the balloon catheters was randomly chosen to be inflated to obtain a desired blood pressure. When a steady-state blood pressure was achieved (within 30 seconds of filling of the balloon), CBF was again determined. The balloon was slowly deflated after the measurements, and the piglet was subsequently allowed to rest for 60 minutes, after which a second baseline CBF was measured during normotension. Twenty minutes later, CBF was measured for the last time after inflating the second balloon-tipped catheter to obtain another desired blood pressure. Thus, each piglet was subjected to hypotension and hypertension, which were induced in a random order. A blood pressure tracing from a typical experiment is depicted in Figure 2. The blood pressures were predetermined to cover a range of mean pressures from 17 to 117 mm Hg. The term blood pressure will refer to mean systemic blood pressure, unless otherwise specified.

Immediately after each microsphere injection and after withdrawal of the reference blood sample, blood was withdrawn from the sagittal vein and left subclavian artery for the determination of blood gases and oxygen saturation of hemoglobin, concentration of hemoglobin, and assays of plasma prostaglandin E (PGE), prostaglandin F₂α (PGF₂α), 6-ketoprostaglandin F₁α (6-keto-PGF₁α), and TXB₂ (the stable metabolite of thromboxane A₂). Withdrawn blood was promptly replaced with blood from a donor piglet. After the experiment, the piglet was killed with pentobarbital. Autopsy was performed to verify the placement of catheters and to remove the brain.

**Measurement of Cerebral Blood Flow**

CBF was measured by the radionuclide-labeled microsphere technique as previously used. Microspheres of 15-μm diameter labeled with [⁴¹Ce], [⁶⁸Sc], [⁵¹Cr], and [⁸⁵Sr] were injected in a random order. Each injection, which contained approximately 300,000 microspheres, was administered into the left ventricle, after which the catheter was flushed with 2 ml saline. Reference blood samples were withdrawn from the left subclavian catheter beginning 10 seconds before microsphere injections and continuing for 70 seconds at a rate of 2 ml/min using an infusion/withdrawal pump (Harvard Apparatus, South Natick, Mass.). Each reference sample contained over 650 microspheres, and each brain region examined (see below) contained more than 2,000 microspheres, regardless of the induced changes in blood pressure. This strongly suggested adequate mixing and distribution of the microspheres. Furthermore, the similarity in the distribution of the radiolabeled microspheres to various areas of the brain also indicated an evenness of mixing of microspheres (CBF of various brain regions is plotted on Figure 3).

Microspheres were injected for CBF determination when blood pressure reached a steady state on four occasions, as described above. The brain was weighed and divided into four major regions: cortex, periventricular area, brain stem, and cerebellum. Radioactivity in the tissues and reference blood samples was counted by a gamma counter (Biogamma II, Beckman Instruments, Inc., Fullerton, Calif.). Energy emitted from each radionuclide was separated using differential spectroscopy by subtracting the percent interference from nuclides. Regional CBF (ml/min/100 g) was calculated using the following formula:

\[
\text{Regional CBF} = \frac{\text{cpm/100 g tissue} \times \text{Ref withdrawal rate}}{\text{cpm in Ref}}
\]
where Ref was the reference blood sample. There was no disproportionate distribution of CBF between the two cerebral hemispheres, as we \textsuperscript{3} and others \textsuperscript{6,10} have previously shown in newborn piglets.

**Assay of Prostaglandins and Thromboxane**

Arterial and sagittal venous blood (1.5 ml) was collected in ice-cold polypropylene tubes containing 28 mg/ml EDTA and 40 \( \mu g/ml \) indomethacin. The blood was immediately centrifuged at 2,450g for 15 minutes at 4\(^\circ\) C. The plasma was stored at -70\(^\circ\) C until the assay. Prostaglandins and thromboxane were measured using radioimmunoassay \textsuperscript{14} kits that were previously tested for reproducibility.\textsuperscript{3} Plasma proteins were precipitated with acetone at -20\(^\circ\) C. Neutral lipids were removed with petroleum ether. The aqueous phase was acidified to pH 3-4. Prostaglandins were extracted with ethyl acetate, which was subsequently evaporated to dryness. The residue was dissolved in a 0.01 M phosphate buffer (pH 7) containing 0.1% bovine gamma globulin and 0.1% sodium azide.

The aliquots of plasma were assayed in duplicate for total PGE, PGF\textsubscript{2\alpha}, 6-keto-PGF\textsubscript{1\alpha}, and TXB\textsubscript{2}. \(^{[3]H}\)Prostaglandins and \(^{[3]H}\)TXB\textsubscript{2} were used for the assays. After an incubation period of 2 hours at 25\(^\circ\) C, the antibody-bound analyte was separated from unbound analyte by dextran-coated charcoal. Biofluor was used as the emulsifier scintillation cock-
tail. Radioactivity was counted in an automated beta scintillation counter (Beckman). All antibodies exhibited less than 1.6\% cross-reactivity to other prostanoids, with the exception of antibodies to PGE, which displayed 100\% cross-reactivity for PGE\textsubscript{1} and PGE\textsubscript{2}. Recovery was determined using aliquots of plasma with known concentrations of prostanoids and was greater than 90\%. The normalized percent bound tracer on standard curves varied less than 5\% between assays. The standards used to determine these curves allowed measurements of concentrations of prostaglandins and thromboxane between 20 and 20,000 pg/ml.

Cerebrovascular production of prostaglandins and thromboxane was calculated as total CBF \( \times \) (sagittal sinus plasma prostanoid concentration - arterial plasma prostanoid concentration) and was expressed in nanograms per minute per 100 g.

**Chemicals and Reagents**

Prostaglandin and thromboxane radioimmunoassay kits were purchased from Advanced Magnetics, Boston, radionuclide-labeled microspheres from 3-M, Newbrighton, Minn., Biofluor from New England Nuclear, Boston, and indomethacin from Sigma Chemical Co., St. Louis. All other chemicals were purchased from Fisher Laboratories, Montreal, Quebec.

**Statistical Analysis**

Data were analyzed using Student's paired and unpaired \( t \) tests, analysis of variance for repeated
avoid adverse hemodynamic effects from the microspheres per se.\textsuperscript{12}

For linear correlation, Pearson's product-moment correlation coefficient ($r$) was calculated. For data exhibiting nonlinearity, the significance of association was tested using nonlinear correlation analysis by calculating Kendall's coefficient of rank correlation ($\tau$), which exhibits greater normal approximation than other rank correlation coefficients.\textsuperscript{16} The best-fit line was determined by using the method of least squares of a polynomial regression analysis and by calculating the coefficient of determination ($R^2$). Stepwise testing was used to assess whether a statistically significant improvement in $R^2$ was achieved after each increase in power of the polynomial function; this procedure thus allowed for determination of the best-fit line of the data points.\textsuperscript{16,17} The best-fit line was established as that having the last sequentially entered polynomial order to produce a significant improvement in $R^2$.\textsuperscript{16,17} Statistical significance was set at $p<0.05$. Values are expressed as mean±SEM, unless otherwise specified.

### Results

**Stability of Experimental Preparations**

Arterial pH, $PO_2$, $PCO_2$, and heart rate remained stable throughout the course of an experiment and did not change with blood pressure (Table 1). Although the heart rate measured immediately after the blood pressure adjustment was inversely related to blood pressure ($r=-0.48; p=0.05$), approximately 30 seconds later during blood flow determination there was no significant relation between heart rate and mean blood pressure ($r=0.29; p=0.19$). This can be appreciated from a typical blood pressure tracing taken from a piglet during one of the experiments and shown in Figure 2. First and second baseline measurements of systolic, diastolic, and mean blood pressure, total and regional CBF, arterial and sagittal sinus prostanoid concentrations, and cerebrovascular production of prostanoids were also not significantly different (Tables 1 and 2).

**Cerebral Blood Flow Autoregulation**

CBF as a function of mean blood pressure is shown in Figure 3 for the total brain, as well as for the cortex, periventricular area, brain stem, and cerebellum. Total and regional CBF were constant between 50 and 90 mm Hg ($r=-0.07$ to 0.36; $p>0.46$) and varied directly with blood pressure below and above this range ($\tau=0.42$ to 0.51; $p<0.05$). A fifth-order polynomial regression was the best fit for all points: $R^2=0.75$ to 0.87 ($p<0.0001$). Regional differences revealed that in the blood pressure range of 50–90 mm Hg the periventricular area exhibited a lower blood flow than total CBF (76±6 and 93±11 ml/min/100 g, respectively; $p<0.05$).

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**Figure 4.** Graphs showing sagittal sinus and arterial blood prostanoid concentrations as a function of mean blood pressure (BP) (graphs a–d) and total cerebral blood flow (CBF) (graphs e–h). PGE, prostaglandin E; 6-keto-PGF$_{1\alpha}$, 6-ketoprostaglandin F$_{1\alpha}$; PGE$_{2\alpha}$, prostaglandin F$_{2\alpha}$; TXB$_2$, thromboxane B$_2$. Sagittal sinus concentrations of prostanoids are displayed as asterisks with solid lines, and arterial blood concentrations are displayed as triangles with dashed lines.
TABLE 1. Arterial pH and Blood Gases and Basal Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Monitored parameters</th>
<th>First basal measurements</th>
<th>Second basal measurements</th>
<th>Hypotension* (17-49 mm Hg)</th>
<th>Hypertension* (91-117 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.41±0.02</td>
<td>7.41±0.03</td>
<td>7.38±0.03</td>
<td>7.40±0.04</td>
</tr>
<tr>
<td>P O₂ (mm Hg)</td>
<td>88.6±8.7</td>
<td>79.5±9.1</td>
<td>76.3±10.3</td>
<td>82.3±10.2</td>
</tr>
<tr>
<td>P CO₂ (mm Hg)</td>
<td>39.6±3.1</td>
<td>38.3±4.4</td>
<td>39.2±3.3</td>
<td>37.8±4.1</td>
</tr>
<tr>
<td>Heart rate† (beats/min)</td>
<td>199±10</td>
<td>207±12</td>
<td>188±7</td>
<td>200±12</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>7.3±4</td>
<td>73±4</td>
<td>(17-49)</td>
<td>(91-117)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>91±7</td>
<td>86±11</td>
<td>(22-55)</td>
<td>(105-150)</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>66±5</td>
<td>69±7</td>
<td>(15-42)</td>
<td>(80-106)</td>
</tr>
<tr>
<td>Cerebral blood flow (ml/min/100 g)</td>
<td>92±18</td>
<td>94±10</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Cortex</td>
<td>89±8</td>
<td>90±11</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Brain stem</td>
<td>99±11</td>
<td>101±11</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>98±6</td>
<td>100±12</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Periventricular area</td>
<td>78±8</td>
<td>73±7</td>
<td>NP</td>
<td>NP</td>
</tr>
</tbody>
</table>

Values are mean±SEM, except for blood pressure (BP), which is also presented as range; n=8. NP, not presented; details in Figure 3.

*Each animal was subjected to one hypotensive and one hypertensive BP change on a random basis.
†Measured during blood flow determinations.

Changes in Cerebrovascular and Arterial Prostanoid Concentrations as a Function of Systemic Blood Pressure

PGE, PGF₂α, 6-keto-PGF₁α, and TXB₂ sagittal venous blood concentrations were significantly correlated with mean blood pressure and total CBF (for prostaglandins, r=−0.52 to −0.66, p<0.001; for TXB₂, r=−0.91 to −0.99, p<0.0001), as seen in Figure 4 (solid lines). Among the various prostaglandins, there were no differences in the correlations of their sagittal sinus concentrations and mean blood pressure and total CBF (Figure 4). The curves displayed a quadratic function for sagittal venous blood prostanoid concentrations versus blood pressure (R²=0.92 to 0.96; p<0.0001) and a third-order polynomial regression for the prostanoid concentrations versus total CBF (R²=0.84 to 0.88; p<0.0001). The concentrations of prostanoids in the cerebral vasculature were lowest between 60 and 90 mm Hg of mean blood pressure and between 75 and 105 ml/min/100 g of CBF, beyond which they increased (Figure 4, panels a–c and e–g). The concentrations of PGE, PGF₂α, and 6-keto-PGF₁α in the sagittal sinus increased by 361±56%, 330±50%, and 301±44%, respectively, when blood pressure was lowered below 50 mm Hg. When blood pressure was raised above 90 mm Hg, the concentrations of PGE and PGF₁α were augmented by 53±9% and 55±8%, whereas those of 6-keto-PGF₁α increased slightly less (37±5%; p<0.05). In contrast, concentrations of TXB₁ remained lowest and did not change above a blood pressure of 60 mm Hg and a total CBF of 75 ml/min/100 g (Figure 4, panels d and h). TXB₂ concentration exhibited the highest increase of all prostanoids during hypotension (658±44%; p<0.05), as shown in Figure 4d.

Prostanoid concentrations in the arterial blood were lower than those in the sagittal sinus (p<0.01), except for concentrations of TXB₂ during blood pressures above 60 mm Hg and total CBF greater than 75 ml/min/100 g (Figure 4, dashed lines; Table 2). Arterial blood prostaglandin concentrations versus total CBF displayed third-order polynomial regressions (R²=0.61 to 0.85; p<0.005). All other regressions of arterial blood prostanoid concentrations versus mean blood pressure and total CBF exhibited quadratic functions (R²=0.63 to 0.91; p<0.005).

Cerebrovascular production of prostaglandins and TXB₂ also correlated with blood pressure (for the

TABLE 2. Basal Sagittal Sinus Prostanoid Concentrations, Arterial Blood Prostanoid Concentrations, and Net Cerebrovascular Production of Prostanoids

<table>
<thead>
<tr>
<th>Sagittal sinus prostanoid concentration (pg/ml)</th>
<th>First basal measurements</th>
<th>Second basal measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGE</td>
<td>1,529±42</td>
<td>1,573±92</td>
</tr>
<tr>
<td>6-keto-PGF₁α</td>
<td>625±24</td>
<td>595±17</td>
</tr>
<tr>
<td>PGF₂α</td>
<td>260±23</td>
<td>266±21</td>
</tr>
<tr>
<td>TXB₁</td>
<td>91±7</td>
<td>101±8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arterial blood prostanoid concentration (pg/ml)</th>
<th>First basal measurements</th>
<th>Second basal measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGE</td>
<td>105±7</td>
<td>121±19</td>
</tr>
<tr>
<td>6-keto-PGF₁α</td>
<td>202±5</td>
<td>231±29</td>
</tr>
<tr>
<td>PGF₂α</td>
<td>146±7</td>
<td>172±28</td>
</tr>
<tr>
<td>TXB₁</td>
<td>119±16</td>
<td>136±24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cerebrovascular production of prostanoids (ng/min/100 g)</th>
<th>First basal measurements</th>
<th>Second basal measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGE</td>
<td>132±9</td>
<td>135±13</td>
</tr>
<tr>
<td>6-keto-PGF₁α</td>
<td>39±7</td>
<td>36±3</td>
</tr>
<tr>
<td>PGF₂α</td>
<td>10±2</td>
<td>11±2</td>
</tr>
<tr>
<td>TXB₁</td>
<td>2±1</td>
<td>1±1</td>
</tr>
</tbody>
</table>

Values are mean±SEM; n=8. PGE, prostaglandin E; 6-keto-PGF₁α, 6-ketoprostaglandin F₁α; PGF₂α, prostaglandin F₂α; TXB₂, thromboxane B₂. Basal measurements were obtained before each adjustment in blood pressure.
prostaglandins, \( r = -0.37 \text{ to } -0.69, p<0.01 \); for TXB\(_2\), \( r = -0.99, p<0.0001 \) and exhibited a sinusoidal-like waveform fifth-order polynomial relation to mean blood pressure \( (R^2=0.41 \text{ to } 0.68; p<0.005) \), as shown in Figure 5. Among the prostaglandins, there was no difference in the correlations between cerebrovascular production and mean blood pressure. Beyond the blood pressure range of 60 and 90 mm Hg, prostaglandin production increased, but it decreased when blood pressure was reduced below 40 mm Hg (Figure 5, panels a–c). In contrast, a net cerebrovascular production of TXB\(_2\) was only observed during hypotension (Figure 5d).

**Discussion**

The main objective of this study was to assess the role of prostanoids in CBF autoregulation in the newborn. For this purpose we determined concentrations and production of prostaglandins and TXB\(_2\) over a blood pressure range of 17–117 mm Hg in newborn piglets.

We altered blood pressure by inflation of balloon-tipped catheters without using pharmacological agents. The observations in this study were in accordance with those of other investigators.\(^2,3,5,18–20\) As indicated in “Materials and Methods,” the use of balloon-tipped catheters does not compromise the accuracy of blood flow measurements with micropipettes. The cerebral hemodynamic values determined in this study are in conformity with data on fetal lambs using a similar approach\(^2\) and neonatal pigs subjected to hemorrhagic hypotension.\(^15\)

Although the heart rate changed immediately after blood pressure adjustments, it stabilized to basal values rather quickly (Table 1), suggesting rapid resetting of baroreceptors.\(^30\) Also, changes in blood pressure did not produce a significant change in blood pH and gases, in conformity with reports of studies using comparable procedures.\(^2,15,29\) Decreases in metabolic rates and anaerobic respiration in response to reductions in oxygen delivery to the tissues have been proposed to explain the maintenance of relatively normal pH after hypotensive and hypoxic insults of short duration in very young animals.\(^27\)

We assayed sagittal sinus blood concentrations of prostanoids because these reflect levels in specific organ vasculature and may better disclose their role as chemical mediators in organ blood flow regulation.\(^31–33\) We have previously shown that serial injections of microspheres do not alter prostanoid concentrations in the sagittal sinus and arterial blood.\(^3\) Also, the sagittal sinus prostanoid concentrations remained stable during the first and second basal measurements (Table 2), and these were similar to those previously reported from the same site,\(^3\) as well as from the cerebral spinal fluid of both acutely and chronically instrumented animals.\(^18,34\) The present data indicate that sagittal sinus prostaglandin concentrations reflect local cerebrovascular production,\(^3\) whereas concentrations of TXB\(_2\) during normotension and hypertension reflect systemic production (Table 2; Figures 4 and 5).

Although CBF was measured when blood pressure had stabilized, prostanoid concentrations were probably changing throughout the hyperemic and ischemic episodes, as previously shown.\(^23,26\) Nonetheless,
cerebrovascular events have been attributed to the cumulative concentrations of prostanoids in the brain during periods of ischemia.19-22,24,25 In addition, the recently reported enhancement in CBF autoregulation in the newborn animal after cyclooxygenase inhibition36 further supports a role for prostanoids in CBF autoregulation.

The increases in cerebrovascular concentration and production of vasodilator prostaglandins, PGE, PGF2α, and prostaglandin I2, observed in this study during a decrease in blood pressure, are possibly the result of an attempt to maintain a constant CBF, as previously suggested.4,6 But concentrations of the vasocostrictr thromboxane,8,19,36 equally potent and effective in young and older animals,57 also increased (Figure 4). Although a summation of the effects of all four prostanoids on the cerebral vasculature would be expected, we speculate that the increase in thromboxane, which is several times more potent than the weaker vasodilator prostaglandins,19,36,38 may have counteracted the action of the prostaglandins and contributed to the decrease in CBF at the lower limit of CBF autoregulation. These data and inferences are supported by other studies that have suggested the participation of thromboxane in the decrease in CBF during hypotension.19-22,25,26

The increases in cerebrovascular prostaglandins observed during hypertension (Figure 4, panels a-c) have been proposed to occur by others7,39 and possibly to enhance CBF autoregulation in the adult.40 Our findings are consistent with reported increases in prostaglandin release during increases in perfusion pressure in ex vivo experiments.41 Stretch of isolated adult cerebral vessels can also evoke a prostanoid-dependent contraction.40 However in contrast to adults, PGE, PGF2α, and prostaglandin I2, which are released by cerebral vessels,8,9 increase CBF in the younger animal.5 Therefore, the hypertension-induced increases only of prostaglandins (Figure 4) may have contributed to the pressure passivity of CBF in the newborn at blood pressures above 90 mm Hg (Figure 3).

The mechanisms of increases of prostanoid concentrations are probably different during hypotension and hypertension.36 PGE, PGF2α, and 6-keto-PGF1α most likely arise from the cerebral vasculature and parenchyma.36 On the other hand, TXB2 is probably produced from platelets and brain parenchyma during tissue ischemia4,21,25,29,43 and minimally produced by the cerebral vasculature,8,5,36 During a sudden decrease in blood pressure, arachidonic acid is released, and its conversion to prostanoids depends upon adequate delivery of oxygen to the tissues.53 The decreases in the production of all prostanoids during cerebral ischemia at blood pressures below 40 mm Hg were probably due to a reduction in tissue oxygenation, leading to a reduction in cyclooxygenase activity.22,23,44

Several vasoactive mediators seem to be involved in the regulation of CBF,45 and these may interact with prostanoids.46,47 But none has explained the mechanisms that determine the range of CBF autoregulation of the newborn animal. Our findings suggest that prostanoids may play a role in CBF autoregulation. It is possible that the blood pressure-dependent changes in plasma prostanoids are coincidental and secondary to changes in CBF.4,6,39,41 However, our recent findings that inhibition of prostanoid synthesis with ibuprofen widened the CBF autoregulatory range of the newborn piglet, both at its upper and lower blood pressure limits,35 support a role for prostanoids in this process.

The findings of this study are relevant in understanding the pathogenesis of ischemic and hemorrhagic encephalopathies of the newborn. We suggest that the increase in concentrations of the cerebral vasodilators PGE2 and PGF2α may limit adequate vasoconstriction necessary for maintaining a constant CBF during elevated blood pressure, in contrast to the situation in the adult.48 Thus, in the newborn, CBF may increase inappropriately during hypertension and lead to distention and ultimately rupture of cerebral blood vessels.49 On the other hand, an increase in the vasoconstrictor thromboxane during hypotension may contribute to ischemic brain insults of the newborn, as suggested for adults.19-22,24,43

In conclusion, cerebrovascular concentrations of PGE, PGF2α, 6-keto-PGF1α, and TXB2 change as systemic blood pressure approaches the limits of CBF autoregulation and exhibit marked blood pressure-dependent changes beyond the limits of autoregulation. These changes in cerebrovascular prostanoids, in concert with their effects on the cerebral vasculature of the newborn,3,4 suggest that prostaglandins and thromboxane may play a role in setting the limits of CBF autoregulation of the newborn animal.

Acknowledgment
We wish to thank Mrs. Inge Blancquart from the Department of Epidemiology and Biostatistics of the Montreal Children's Hospital Research Institute for her tremendous assistance in the statistical analysis of the data.

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**KEY WORDS** prostanoids • thromboxane • cerebral blood flow autoregulation • newborn
Changes in cerebrovascular prostaglandins and thromboxane as a function of systemic blood pressure. Cerebral blood flow autoregulation of the newborn.
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Circ Res. 1990;67:674-682
doi: 10.1161/01.RES.67.3.674
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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