Enhanced Cerebral Blood Flow Autoregulation in the Newborn Piglet by d-Tubocurarine and Pancuronium but Not by Vecuronium

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Neuromuscular blockers may affect cerebral blood flow (CBF) regulation in the newborn. We studied the effects of d-tubocurarine (0.1 mg·kg⁻¹, n = 8), pancuronium (0.1 and 0.4 mg·kg⁻¹, n = 6 and 7), and vecuronium (0.1 and 0.4 mg·kg⁻¹, n = 6 and 7) on CBF measured over the same range of mean systemic blood pressure (BP) 15–122 mmHg in each group of newborn pigs controls received normal saline (n = 7). The levels of BP during hypotension and hypertension were scaled at intervals of 5 ± 1.6 mmHg and adjusted by inflating balloon-tipped catheters placed in the aorta. After saline, the low dose of pancuronium (0.1 mg·kg⁻¹), and the two doses of vecuronium, CBF was constant over the BP range of 50–90 mmHg (r = −0.07–0.35, P > 0.20) but varied directly with BP beyond this range (r = 0.38–0.60, P < 0.05). In contrast, in pigs treated with d-tubocurarine and high-dose pancuronium, CBF remained constant from 35 to 122 mmHg of BP (r = 0.14–0.37, P > 0.10) and changed minimally (4–12%) with BP > 105 mmHg compared to the other groups (41–59%, P < 0.01). When BP was reduced below 30 mmHg, CBF also decreased less (20–38%) in animals treated with d-tubocurarine and high dose-pancuronium than after the other treatments (58–67%, P < 0.05). CBF autoregulation was also depressed in pigs treated with the ganglion blocker, hexamethonium (1 mg·kg⁻¹, n = 6); the relation between CBF and BP in these animals was almost identical to that observed with the muscarinic blocking agents, d-tubocurarine and high-dose pancuronium. Hexamethonium, d-tubocurarine, and high-dose pancuronium did not alter the other treatments attenuated the baroreceptor-mediated BP response to common carotid artery occlusion. In summary, neuromuscular blocking agents with ganglionic blocking activity (d-tubocurarine and high-dose pancuronium) as well as the specific ganglion blocker hexamethonium enhanced CBF autoregulation, but agents more selective for the neuromuscular junction (pancuronium and low-dose pancuronium) did not alter CBF autoregulation of the newborn pig. (Key words: Brain; blood flow. Neuromuscular relaxants, nondepolarizing; pancuronium; d-tubocurarine; vecuronium. Swine; newborn. Sympathetic nervous system, ganglion blockers: hexamethonium.)

NEUROMUSCULAR BLOCKERS are often used in neonates to facilitate ventilation.1 Peabody2 observed that cerebral blood flow (CBF) velocity increased in sick newborn infants who received d-tubocurarine or pancuronium. More importantly, it has also been reported that pancuronium can attenuate the fluctuations in the CBF velocity pattern observed in neonates with respiratory distress syndrome.2,3 Since fluctuations in CBF predispose to intraventricular hemorrhage,4,5 neuromuscular blockers may prevent the development of this neurologic insult.6

Neuromuscular blockade may affect cerebral hemodynamics as a result of changes in blood gases from improved ventilation and/or mean airway pressure during ventilation.5,6 However, a number of neuromuscular blockers can also block ganglionic nicotinic receptors7–9 and alter the activity of the autonomic nervous system, which is known to play an important role in CBF regulation.10–14 Furthermore, pancuronium has also been shown to cause a release of catecholamines,15 which themselves may alter cerebral hemodynamics.12,16 Whether or not neuromuscular blockers can specifically affect CBF autoregulation, particularly in the newborn, by a mechanism independent of changes in blood gases, has not been investigated.

We therefore studied the effects of d-tubocurarine, pancuronium, and vecuronium on cerebral hemodynamics over a wide range of systemic blood pressure (BP) in normoxic and normocapnic newborn piglets. The results show that neuromuscular blockers that possess ganglionic-blocking activity increase the range of BP over which CBF autoregulation occurs.

Materials and Methods

Surgical Preparation

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

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The experimental methods used were similar to those we previously described in detail.\textsuperscript{17,18} Fifty-four 1–3-day-old newborn piglets (1.6–2.4 kg) were studied. The animals were anesthetized with 0.5% halothane for tracheotomy and for catheterization of the blood vessels. Catheters (Argyle, 3½-Fr) were placed into the left subclavian artery for the injection of radioactive labeled microspheres and into the left subclavian artery for BP recording and for withdrawal of blood samples. A silicone-coated balloon-tipped catheter fenestrated near its end (Berman Angiocath, 5-Fr) was introduced into the right common carotid artery and placed in the ascending aorta immediately distal to the root of the aorta. In the newborn pig, ligation of one carotid artery does not modify CBF,\textsuperscript{17–19} and the limits of CBF autoregulation are similar to those of newborn animals with intact carotid arteries.\textsuperscript{17,20,21} By filling the balloon at the aortic root, hypotension was produced in the aortic arch, and its fenestrations enabled BP to be continuously recorded in the aortic arch using a Statham pressure transducer connected to a multichannel recorder (Gould, Cleveland, OH). A second balloon-tipped catheter was introduced into the thoracic descending aorta \textit{via} a femoral artery. Filling of this balloon produced hypertension in the aortic arch. A polyethylene catheter (Intramedic, PE-50) was placed in the femoral vein for injection of drugs. A similar catheter (PE-50) was inserted into the sagittal sinus through a burr hole in the skull for pressure measurements, which did not significantly change during normotension, hypotension, and hypertension (mean ± SEM: 5 ± 2, 4 ± 2, and 5 ± 1 mmHg, respectively) for all groups studied.

Halothane was discontinued after surgery. Immediately thereafter, α-chloralose (initially 50 mg·kg\textsuperscript{-1} intravenously, followed by 10 mg·kg\textsuperscript{-1}·hr\textsuperscript{-1} intravenously) was administered and maintained throughout the experiment. The lungs of the animals were ventilated (Harvard small animal respirator) with a gas mixture of 25% oxygen and 75% nitrogen. After being placed under a radiant warmer to keep their body temperature at 38° C, the animals were allowed to recover from the surgery for 2–3 h. Brain temperature was not measured and most likely did not change significantly over the short duration of BP change (< 2 min).

**Experimental Protocol**

Fifteen minutes before the first CBF measurement was taken, animals were randomly assigned to receive intravenously either normal saline (controls, n = 7), d-tubocurarine (0.1 mg·kg\textsuperscript{-1}, n = 8), pancuronium (0.1 mg·kg\textsuperscript{-1}, n = 6; or 0.4 mg·kg\textsuperscript{-1}, n = 7), or vecuronium (0.1 mg·kg\textsuperscript{-1}, n = 6; or 0.4 mg·kg\textsuperscript{-1}, n = 7). This time interval was chosen because stable hemodynamic parameters have been shown to be achieved rapidly after administration of the drugs.\textsuperscript{2,22} The doses selected effectively paralyzed the piglets and corresponded to ones often used in the neonate.\textsuperscript{1}

Ten minutes after baseline measurements were obtained, one of the balloon catheters was randomly chosen to be inflated to a desired BP. When steady-state BP was achieved, CBF was measured again. BP was previously shown to reach steady-state values within 50 s of filling of the balloon.\textsuperscript{17} In preliminary experiments we established that CBF also reached stability within 90 s of balloon inflation; this was demonstrated by continuously measuring anterior cerebral artery blood flow velocity (Medisons D10) using a Doppler pencil probe (8 MHz) applied to the dura, as previously described\textsuperscript{23} and shown to reflect CBF in the newborn pig and human.\textsuperscript{23,24}

After CBF had been measured, the balloon was slowly deflated and the animal was allowed to stabilize for 60 min. As most animals recovered from paralysis, a repeat dose of the drug was administered 15 min before a second baseline CBF was measured during normotension. Ten minutes later, CBF was measured for the last time after inflating the second balloon-tipped catheter to another desired BP. Thus, each animal was subjected to one level of hypotension and one of hypertension, induced in a random order. For each group the levels of BP during hypotension and hypertension were scaled at intervals of 5 ± 1.6 mmHg, such that for all of the treatment groups CBF would be measured over the same range of BP, 15–122 mmHg; there was no difference between the groups for any of the BP levels (P > 0.35 by analysis of variance [ANOVA]).

Following withdrawal of the reference blood sample after microsphere injection, blood was also withdrawn for determination of blood gases. Withdrawn blood was promptly replaced with blood from a donor piglet. After the experiment the animal 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 using the radionuclide-labeled microsphere technique\textsuperscript{25} as previously described.\textsuperscript{17,18} Microspheres of 15-μm diameter labeled with \textsuperscript{141}Ce, \textsuperscript{51}Cr, and \textsuperscript{85}Sr were injected in random order. Each injection, which contained approximately 300,000 microspheres, was administered into the left subclavian artery, after which the catheter was flushed with 2 ml normal saline. Reference blood samples were withdrawn from the left subclavian catheter beginning 10 s prior to microsphere injections, and withdrawal was continued for a total of 70 s at a rate of 2 ml·min\textsuperscript{-1} using a Harvard infusion/withdrawal pump. Each reference sample contained more than 600 microspheres, and each brain region examined (see
below) contained more than 1,900 microspheres, regardless of the induced changes in BP. This and the similarity in the distribution of the radionuclide microspheres to various areas of the brain (see CBF of various brain regions, fig. 1) strongly suggested adequate mixing and distribution of the microspheres.  

The brain was weighed and divided into three major regions: cerebrum, brainstem, and periventricular area. Radioactivity in the tissues and reference blood samples was counted using a γ counter (Beckman, Biogamma II). Energy emitted from each radionuclide was separated using differential spectroscopy by subtracting the percent interference between nuclides. Regional CBF (milliliters per minute per 100 g) was calculated using the following formula: regional CBF = cpm/100 g tissue × reference blood sample withdrawal rate/cpm in reference blood sample. There was no disproportionate distribution of CBF between the two cerebral hemispheres, as we17,18 and others have previously shown in newborn piglets.19  

Cerebrovascular resistance (CVR, in mmHg·min·100 g·ml⁻¹) also was calculated, as mean systemic BP/CBF.  

**ASSESSMENT OF GANGLIONIC BLOCKADE BY NEUROMUSCULAR BLOCKERS**  

To examine the blocking activity of neuromuscular blockers on autonomic ganglion nicotinic receptors, we studied the baroreceptor-mediated BP response to common carotid artery occlusion.9 In seven newborn pigs, silk strings were placed around both common carotid arteries and the femoral arterial BP response to 30 s of common carotid artery occlusion was recorded before and after the administration of the neuromuscular blockers and the ganglionic blocker hexamethonium (1 mg·kg⁻¹ intravenously).  

The effects of neuromuscular blockers on CBF autoregulation (see Results section) were also compared to those of hexamethonium (1 mg·kg⁻¹ intravenously) in six other piglets.  

**CHEMICALS AND REAGENTS**  

Radionuclide-labeled microspheres were purchased from New England Nuclear (Boston, MA), pancuronium and vecuronium from Organon Inc. (West Orange, NJ), d-tubocurarine from Quad Pharmaceuticals (Indianapolis, IN), and hexamethonium from Sigma Chemical Co. (St. Louis, MO).  

**STATISTICAL ANALYSIS**  

Data were analyzed using Student’s paired and unpaired t tests; ANOVA for repeated measures; tests for comparison among means; and linear and nonlinear correlation and regression analysis, as previously described in detail.17,18  

For linear correlation, the 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, τ, which exhibits greater normal approximation than other rank correlation coefficients.26 The best fit line was determined using the method of least squares of a polynomial regression analysis, and by calculating $R^2$, the coefficient of determination.26,27  

Because BPs were predetermined and similar for all groups, CBF was also analyzed by two-way ANOVA, factoring for group and BP state (normotension, hypotension, or hypertension); significant differences in CBF between and within groups were found and were consistent with those described in the Results section (fig. 1). The data for each group were combined to construct the regression curves, which were analyzed according to

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**Fig. 1.** Effects of neuromuscular blockers on regional cerebral blood flow (CBF) as a function of mean blood pressure (BP) in newborn piglets. The asterisks with the solid line refer to the cerebrum; the empty triangles with closely spaced dashes refer to the brainstem; and the empty circles with widely-spaced dashes refer to the periventricular area.
NEUROMUSCULAR BLOCKERS AND CEREBRAL BLOOD FLOW

Cerebral Blood Flow Autoregulation

CBF as a function of mean BP is shown in figure 1 for the cerebrum, brainstem, and periventricular area. CBF correlated non-linearly with mean BP (r = 0.49–0.68, P < 0.01) after treatment of animals with normal saline, the low dose of pancuronium (0.1 mg·kg⁻¹), and both low and high doses of vecuronium (0.1 and 0.4 mg·kg⁻¹). CBF was constant between 50 and 90 mmHg of BP (r = −0.07 to 0.35, P > 0.20) and varied directly with BP below and above this range (r = 0.38–0.60, P < 0.05). A fourth- or fifth-order polynomial regression fitted best all points (R² = 0.84–0.98, P < 0.0001).

In contrast to the effects of vecuronium and the low dose of pancuronium, treatment with d-tubocurarine and the high dose of pancuronium (0.4 mg·kg⁻¹) increased the CBF autoregulatory range. Regional CBF remained constant between 35 and 122 mmHg of BP (r = 0.14–0.37, P > 0.10) and varied with BP below this range (r = 0.37–0.65, P < 0.05); a third-order polynomial regression fitted best the points (R² = 0.65–0.92, P < 0.001). In addition, when BP was reduced to its lowest levels (< 30 mmHg), the decrease in CBF was only 20–38% in d-tubocurarine- and high-dose pancuronium-treated animals, and significantly less (P < 0.05) than the decrease in the other groups (58–67%). Furthermore, in animals treated with d-tubocurarine and the high dose of pancuronium, CBF exhibited minimal increases (4–12%) when BP was raised to its highest levels (> 105 mmHg); this increase was less (P < 0.01) than that found in the other groups of animals (41–59%).

In all groups, regional CBF differences revealed that in the BP range of 50–90 mmHg the periventricular area exhibited a lower blood flow than that to the cerebrum and brainstem (P < 0.05) (fig. 1).

In order for CBF to remain constant when BP increases, CVR must increase. Therefore, the relationship between CVR and BP was examined for BP ranges within and beyond the limits of CBF autoregulation (fig. 2), according to the results presented above. In animals treated with normal saline, the low dose of pancuronium, and both doses of vecuronium, CVR correlated positively with mean BP only in the range of 50–90 mmHg (r = 0.67–0.90, P < 0.01), and neither beyond this range (r = −0.66–0.31, P > 0.15) nor over the full range of BP studied (r = −0.08–0.34, P > 0.1). In contrast, in piglets treated with d-tubocurarine and the high dose of pancuronium, CVR correlated significantly with mean BP over the entire range of BP studied (r = 0.99 and 0.90, P < 0.0001). These findings on CVR confirm those obtained for CBF.

RESULTS

Stability of Experimental Preparations

Arterial pH, P_{CO₂}, and P_{O₂} remained stable throughout the course of an experiment and did not change with BP in all groups studied (table 1). First and second baseline measures of mean BP and CBF also were not significantly different from each other in any experiment as well as between experiments on different animals.

![Fig. 2. Relationship between cerebrovascular resistance (CVR) and mean blood pressure (BP) after administration of neuromuscular blockers to newborn piglets.](image-url)
### Table 1. Arterial pH and Blood Gases and Basal Hemodynamic Parameters

<table>
<thead>
<tr>
<th></th>
<th>First Basal Measurements</th>
<th>Second Basal Measurements</th>
<th>Hypotension* (&lt;50 mmHg)</th>
<th>Hyperension* (&gt;90 mmHg)</th>
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<td><strong>Controls</strong></td>
<td></td>
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<td></td>
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<tr>
<td>$\rho$H</td>
<td>$7.40 \pm 0.03$</td>
<td>$7.37 \pm 0.02$</td>
<td>$7.36 \pm 0.03$</td>
<td>$7.37 \pm 0.02$</td>
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<td>$P_{CO_2}$ (mmHg)</td>
<td>$40 \pm 6$</td>
<td>$42 \pm 7$</td>
<td>$41 \pm 4$</td>
<td>$38 \pm 6$</td>
</tr>
<tr>
<td>$P_{O_2}$ (mmHg)</td>
<td>$89 \pm 9$</td>
<td>$87 \pm 9$</td>
<td>$89 \pm 8$</td>
<td>$84 \pm 7$</td>
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<td>Mean BP (mmHg)</td>
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<td>$74 \pm 7$</td>
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<td>$7.37 \pm 0.02$</td>
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<td>$P_{CO_2}$ (mmHg)</td>
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<tr>
<td>$P_{O_2}$ (mmHg)</td>
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<td>$97 \pm 8$</td>
<td>$87 \pm 8$</td>
<td>$88 \pm 7$</td>
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<tr>
<td>Mean BP (mmHg)</td>
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<td>$69 \pm 7$</td>
<td>$15-49$</td>
<td>$91-119$</td>
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<tr>
<td>Total CBF (ml·min⁻¹·100 g⁻¹)</td>
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<td>$91 \pm 13$</td>
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<tr>
<td><strong>Pancuronium (0.1 mg·kg⁻¹)</strong></td>
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<td>$7.38 \pm 0.03$</td>
<td>$7.37 \pm 0.02$</td>
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<td>$P_{CO_2}$ (mmHg)</td>
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<td>$41 \pm 4$</td>
<td>$38 \pm 6$</td>
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<td>$P_{O_2}$ (mmHg)</td>
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<td>Total CBF (ml·min⁻¹·100 g⁻¹)</td>
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<td>$7.36 \pm 0.03$</td>
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<td>$104 \pm 10$</td>
<td>$92 \pm 10$</td>
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<td>Mean BP (mmHg)</td>
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<td>$69 \pm 9$</td>
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<td>Total CBF (ml·min⁻¹·100 g⁻¹)</td>
<td>$89 \pm 5$</td>
<td>$87 \pm 6$</td>
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<tr>
<td>Total CBF (ml·min⁻¹·100 g⁻¹)</td>
<td>$87 \pm 5$</td>
<td>$83 \pm 6$</td>
<td>NP</td>
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</table>

Values are mean ± SEM, except for mean blood pressure (BP), which is also presented as range; n = six to eight animals per group. NP = not presented; details on cerebral blood flow (CBF) are in figure 1.

* Each animal was subjected to one hypotensive and one hypertensive blood pressure change on a random basis.

### Effects of Hexamethonium on Cerebral Blood Flow Autoregulation

Hexamethonium caused a slight but significant decrease in BP, to $54 \pm 5$ and $57 \pm 3$ mmHg, measured during the first and second basal measurements, respectively ($P < 0.05$). However, the first and second basal CBF measurements ($94 \pm 12$ and $87 \pm 4$ ml·min⁻¹·100 g⁻¹) were similar to those of the other groups. The relation between CBF and BP in hexamethonium-treated animals was virtually superimposable on that observed in animals treated with d-tubocurarine and high-dose pancuronium (fig. 3). The data fitted best a third-order polynomial regression ($R^2 = 0.81$, $P < 0.0001$), with CBF constant between 35 and 119 mmHg of mean BP ($r = 0.36$, $P = 0.13$). Furthermore, when BP was reduced to its lowest levels there was a similar decrease in CBF ($92 \pm 4\%$) to that seen after d-tubocurarine and high-dose pancuronium ($26 \pm 7\%$ and $36 \pm 6\%$, respectively, $P > 0.25$). CVR correlated linearly with mean BP over the entire range of BP studied ($r = 0.88$, $P < 0.0001$).

### Effect of Neuromuscular Blockers on Baroreceptor-Mediated Blood Pressure Responses

The pressor response to common carotid artery occlusion after saline was $20-26$ mmHg (mean BP) and was changed neither by the low dose (0.1 mg·kg⁻¹) of pancuronium and nor by the low and high doses (0.1 and 0.4 mg·kg⁻¹) of vecuronium. d-Tubocurarine, the high dose (0.4 mg·kg⁻¹) of pancuronium, and hexamethonium suppressed the baroreceptor-mediated mean BP response to $\pm 10$ mmHg (fig. 4).
FIG. 3. Comparison of changes in total cerebral blood flow (CBF) as a function of mean blood pressure (BP) after administration of normal saline (controls), \(d\)-tubocurarine, pancuronium, and hexamethonium to newborn piglets. For clarity, symbols are indicated only for hexamethonium-treated pigs; details for the other treatment groups are in figure 1.

**Discussion**

To determine the effects of neuromuscular blockers on CBF autoregulation, CBF was measured over a wide range of systemic BP. We altered BP using nonpharmacologic means by inflation of balloon-tipped catheters. The cerebral hemodynamic values obtained are in conformity with data on fetal lambs and neonatal pigs using similar as well as different protocols.\(^{17,18,20-22,28}\) Blood pH and gases also remained stable during the experiments, in accordance with studies using similar procedures.\(^{17,18,21}\)

As described previously, CBF autoregulation of the adult is composed of an acute and rapid phase of onset that occurs within a few seconds of a BP adjustment, followed by a second phase of increased CVR that may last 2–4 min until CBF reaches its resting value.\(^{29,30}\) Some of these observations made by certain investigators are questionable given that CBF was not continuously measured (\(^{65}\)Kr injections).\(^{30}\) Furthermore, a careful analysis of data by others who measured CBF with electromagnetic flow probes placed around the internal carotid artery, which supplies blood to most of the brain, reveals that CBF appears to stabilize almost completely within the first minutes following a change in BP\(^{25}\); a subsequent slight increase in CVR may have been secondary in part to the barbiturates used,\(^{20}\) which can cause a gradual enhancement of CBF autoregulation.\(^{31}\) Most importantly, we established in preliminary experiments in the newborn animal that CBF velocity, which reflects CBF,\(^{23,24}\) reached stability within 50 s of a BP change. Our findings are in accordance with those of others in the adult\(^{29}\) and indicate that the cerebral vasculature responds and CBF becomes set within seconds of a change in BP.\(^{32,33}\) Therefore, our CBF measurements, taken 30 s after an adjustment in BP, were reliable.

In the newborn animal, CBF remains constant between 50 and 90 mmHg of BP and varies with BP below and above this range.\(^{17,18,21}\) The effects of neuromuscular blockers on CBF autoregulation of the newborn piglet varied depending on the agents tested and their doses (figs. 1 and 2). \(d\)-Tubocurarine and the high dose of pancuronium (0.4 mg·kg\(^{-1}\)) widened the CBF autoregulatory range, whereas the low dose of pancuronium (0.1 mg·kg\(^{-1}\)) and both doses of vecuronium (0.1 and 0.4 mg·kg\(^{-1}\)) did not. The basal CBF was not affected by any of the agents as previously described for pancuronium and \(d\)-tubocurarine.\(^{22,28}\)

Our conclusions regarding comparisons for the range of CBF autoregulation among the groups studied are based on several observations and analyses. 1) The percent changes in CBF from baseline values during increases and decreases in BP above and below, respectively, the normal range of CBF autoregulation (controls) were significantly less in animals treated with \(d\)-tubocurarine, high-dose pancuronium, and hexamethonium than in the other groups (\(P < 0.05\)). 2) Since the BPs were predetermined

FIG. 4. Tracings of blood pressure (BP) response to common carotid artery occlusion after treatment of newborn piglets with normal saline, hexamethonium, \(d\)-tubocurarine, pancuronium, and vecuronium. The intravenous doses indicated next to the drugs are expressed in milligrams per kilogram.
and similar for all groups, CBF was also analyzed by two-way analysis of variance factoring for group (intersubject analysis) and BP status (normo-, hypo- [< 30 mmHg], or hypertension [> 105 mmHg]); intrasubject analysis). Significant differences in CBF between and within groups were found and were consistent with those described (see Results section and fig. 1). Of great importance in interpreting CBF autoregulation data is the relation between CVR and BP. In order for CBF to remain constant when BP increases, CVR must increase. Indeed, CVR increased over the entire and same range of BP in animals treated with d-tubocurarine, high-dose pancuronium, and hexamethonium but not in those treated with saline, the low dose of pancuronium, or either dose of vecuronium. Thus, the correlation between CVR and BP was significantly different than 0 (P < 0.0001) for animals treated with d-tubocurarine, high-dose pancuronium, and hexamethonium but not for the others (P > 0.1) (fig. 2). Consequently, CBF remained constant over a wide range of BP in newborn pigs after treatment with d-tubocurarine, high-dose pancuronium, and hexamethonium (r = 0.14 – 0.37, P > 0.1) (figs. 1 and 3). Therefore it is appropriate to conclude that d-tubocurarine, high-dose pancuronium, and hexamethonium enhanced CBF autoregulation of the newborn pig.

Vecuronium and low doses of pancuronium are selective for the nicotinic neuromuscular receptor site.7 The absence of effects of these drugs on CBF autoregulation (figs. 1C, 1D, and 1E, and 2C, 2D, and 2E) and on the baroreceptor-mediated pressor response (fig. 4) concurs with their selectivity. Thus, the reduction in CBF velocity fluctuations previously reported with pancuronium (0.1 mg · kg⁻¹)₂,₃ cannot be explained on the basis of an enhancement in CBF autoregulation independent of changes in blood gases; however, higher doses may have contributed to this phenomenon (figs. 1C and 1D). Furthermore, the effect of d-tubocurarine in widening CBF autoregulation at the doses given (0.1 mg · kg⁻¹) (fig. 1B) may partly account for the reduction in CBF velocity fluctuations seen in sick newborns.² Thus, d-tubocurarine and high-dose pancuronium, which exhibit lesser selectivity for the neuromuscular junction,⁷,₃⁴ may enhance CBF autoregulation in the newborn. Such an enhancement in CBF autoregulation may protect neonates from developing intraventricular hemorrhages,⁵,₄ but the efficacy of these drugs for this purpose remains to be confirmed.

The mechanisms by which neuromuscular blockers can produce their effects on CBF autoregulation remain to be elucidated. Although it was not the primary aim of this study, certain speculations can be made with regard to the differences observed between the effects of d-tubocurarine and high-dose pancuronium and the effects of vecuronium and low-dose pancuronium on CBF autoregulation. These quaternary ammonium compounds do not cross the blood–brain barrier.⁹ Therefore, the differences in their effects must be of peripheral origin. d-Tubocurarine can cause the release of histamine and of prostacyclin,¹⁴,³⁵ known to vasodilate cerebral vessels.⁵⁷,³⁸ Although this cerebral vasodilatory effect may have explained the maintenance of CBF during hypotension after d-tubocurarine, neither a decrease in basal BP nor an increase in basal CBF was detected after administration of this drug (table 1). Pancuronium, on the other hand, causes minimal, if any, release of histamine.⁷,³⁴,³⁹ Thus, it is unlikely that histamine and prostacyclin contributed to setting the lower limit of CBF autoregulation to a lower BP after administration of d-tubocurarine and pancuronium.

The principal action of neuromuscular blockers is to block the nicotinic receptor site at the neuromuscular junction.⁷ However, neuromuscular blockers with lesser selectivity at this site, such as d-tubocurarine and high or cumulative doses of pancuronium, can also inhibit autonomic ganglion nicotinic receptors and consequently affect circulation.⁷–⁹,¹⁶ A suppression of baroreceptor-mediated pressor response by d-tubocurarine and high-dose pancuronium suggests that these agents blocked autonomic ganglia under the present experimental conditions (fig. 4). During hypotension and decreased perfusion pressure, sympathetic activity increases to maintain systemic BP.¹⁶,⁴⁰ An increase in sympathetic nerve activity has been shown to decrease CBF and pial artery diameter in the newborn animal.¹₅ Inhibition of sympathetic activity, surgically, or pharmacologically by using ganglionic blockers, causes an increase in CBF during adaptive physiologic conditions.¹₆,⁴¹ However, basal CBF does not seem to be altered by ganglionic blockade.⁷ Our findings support these inferences. d-Tubocurarine and high-dose pancuronium inhibited autonomic ganglia (fig. 4) and maintained a higher CBF during hypotension without modifying basal CBF (figs. 1B and 1D; table 1); these effects were nearly identical to those of the ganglionic blocker hexamethonium (figs. 3 and 4). During hypertension, d-tubocurarine and high-dose pancuronium maintained CBF constant to the upper limit of BP measured (figs. 1B and 1D). Thus, CBF increased as BP increased (figs. 2B and 2D). The mechanism responsible for this effect is not clear. Pancuronium has been shown to cause postganglionic nerve endings to release of noradrenaline,¹⁷ which may increase CVR.¹² However, the absence of any changes in BP after pancuronium (table 1) tends to dismiss this possibility.

It has been suggested that the upper limit of CBF autoregulation is mostly under myogenic control.¹⁰,¹¹ However, this opinion is not shared by all authors,²⁹,⁴² and other mechanisms have also been implicated.¹₁,¹₃,¹₄,¹₈,⁴₂,⁴₃ Within the limits of CBF autoregulation, increases in arterial BP produce a sympathetic innervation-dependent
cerebral vasoconstriction, which contributes to maintain CBF constant during hypertension. When BP increases to levels greater than the CBF autoregulatory range, sympathetic activity becomes insufficient to maintain CBF constant; in conjunction, there is an augmentation in parasympathetic nerve activity, which itself causes an increase in CBF. It is of interest that atropine, which can also produce parasympathetic ganglion blockade, prevents hypertensive-induced increases in CBF in the newborn pig. Moreover, during hypertension, newborn pigs that have undergone cervical sympathetic denervation exhibit a greater rise in CBF compared to innervated ones. Thus, we speculate that inhibition of parasympathetic activity by inducing ganglionic blockade, with hexamethonium as well as with d-tubocurarine and high-dose pancuronium (fig. 4) prevented the increase in CBF during hypertension seen in control animals (figs. 1B, 1D, and 3). Our findings and inferences are consistent with those of others who have shown an attenuation in the increase in CBF during acute severe hypertension after parasympathetic lesion and trigeminallectomy. In the absence of autonomic nervous system activity after ganglionic blockade, it remains to be determined which factors cause CBF to remain constant and hence CVR to increase during acute hypertension (figs. 1–3).

In summary, d-tubocurarine, pancuronium, and vecuronium had no effect on basal CBF of the newborn piglet. However, during adaptive physiologic conditions, such as during BP changes, neuromuscular blockers with autonomic ganglion blocking activities (d-tubocurarine and high-dose pancuronium) widen the CBF autoregulatory range, as was also the case with the ganglionic blocking agent hexamethonium. In contrast, neuromuscular blockers that are more selective for the neuromuscular junction (vecuronium and low-dose pancuronium) had no effect on CBF autoregulation.

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The references:

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