

Impairment of Cerebral Autoregulation during Extracorporeal Membrane Oxygenation in Newborn Lambs

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ABSTRACT. This study was designed to evaluate the effect of normothermic partial bypass, or venoarterial extracorporeal membrane oxygenation (ECMO), on cerebral autoregulation. Fourteen newborn lambs, 1–7 d of age, were randomized into two groups: control (ligation of right carotid artery and jugular vein without ECMO; $n = 7$) and ECMO (ligation with placement on routine venoarterial ECMO at 120–150 mL/kg/min; $n = 7$). After 1 h of ECMO or stabilization in controls, cerebral autoregulation was evaluated by lowering cerebral perfusion pressure (CPP) by increasing intracranial pressure through infusion of artificial cerebrospinal fluid into the lateral ventricle. Four ranges of CPP were evaluated: 1) baseline, 2) 55–40, 3) 39–25, and 4) <25 mm Hg. In ECMO animals, cerebral blood flow (CBF) decreased from baseline (39 ± 7 mL/100 g/min) to 23 ± 7 and 12 ± 2 at CPP of 39–25 and <25 mm Hg. In the control group, CBF was unchanged from baseline (48 ± 11 mL/100 g/min) until CPP was <25 mm Hg, at which time it decreased to 27 ± 16 mL/100 g/min. Cerebral oxygen consumption decreased from baseline (4.2 ± 1.1 mL/100 g/min) to 4.0 ± 0.7 and 3.2 ± 1.3 mL/100 g/min at CPP of 39–25 and <25 mm Hg, respectively, in the ECMO group. In the control group, cerebral oxygen consumption was unchanged from baseline (4.2 ± 1.1 mL/100 g/min) until CPP was reduced to <25 mm Hg (3.2 ± 1.3 mL/100 g/min). When CBF autoregulation was altered, i.e. when total CBF decreased, right-left hemispheric CBF differences were noted in both groups. These findings show that venoarterial ECMO, at flow rates of 120–150 mL/kg/min, alters cerebral autoregulation in healthy newborn lambs and that, if CBF is decreased by an increase in intracranial pressure, carotid artery ligation can result in lower CBF on the ipsilateral side. (*Pediatr Res* 33: 289–294, 1993)

Abbreviations

CBF, cerebral blood flow
CMRO₂, cerebral oxygen consumption
CPB, cardiopulmonary bypass
CPP, cerebral perfusion pressure
CSF, cerebral spinal fluid
E, cerebral fractional oxygen extraction
ECMO, extracorporeal membrane oxygenation
ICP, intracranial pressure
MAP, mean arterial pressure
OT, cerebral oxygen transport

PaO₂, arterial oxygen pressure

PACO₂, arterial carbon dioxide pressure

Autoregulation of the cerebral circulation is an important homeostatic mechanism that maintains CBF over a wide range of CPP (1–3). The presence of cerebral autoregulation has been demonstrated in adult humans and in adult, newborn, and fetal animals (1–4). Systemic insults such as severe asphyxia, hypoxia, and hypercarbia can disrupt cerebral autoregulation leaving the cerebral microcirculation vulnerable to alterations in systemic blood pressure (1, 2, 5). In this state, hypotension can result in ischemic cerebral damage, whereas hypertension can cause cerebral hyperemia and thus the risk for cerebral hemorrhage.

Therapies such as hypothermic CPB have been shown to impair cerebral autoregulation in some studies (6, 7) but not in others (8, 9). These contradictory findings are related to differing use of hypothermia and acid-base blood gas management during CPB (9). To date, no studies have evaluated the effect of normothermic partial CPB or ECMO on cerebral autoregulation. Because the major cause of death in the ECMO population is intracranial hemorrhage, a full understanding of the effect of ECMO on the cerebral circulation is indicated (10, 11). The present study was designed to assess the effect of venoarterial ECMO on cerebral autoregulation in the healthy newborn lamb (12).

MATERIALS AND METHODS

Subjects. Fourteen anesthetized lambs of mixed breed, 1–7 d of age, were used for the study.

Surgical procedures. Lambs were anesthetized with pentobarbital (10–20 mg/kg) before surgery and then maintained on a drip (3 mg/kg/h) throughout the remainder of the study. Catheters were placed in the right femoral artery and vein for blood pressure monitoring, i.v. fluid, and medication administration. The microsphere reference catheter was placed in the left lingual artery for both groups, with the microsphere injection catheter placed in the left ventricle, verified by pressure wave forms, in the controls only. To gain access to the superior sagittal sinus, the skull was entered in the midline approximately 1 cm anterior to the lambda sutures. The sagittal sinus was identified, and the overlying dura was punctured with a 19-gauge needle. The catheter tip was placed proximal to the confluence of sinuses to obtain sagittal sinus blood for analysis of cerebral venous blood gases and pressure monitoring. The lateral ventricle was cannulated by drilling a hole through the skull about 5 mm lateral to the midline between coronal and lambda sutures. The ventricular catheter was advanced into the lateral ventricle with placement

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verified by the free flow of CSF. The site of placement of the ventricular catheter was alternated so that an equal number of right and left catheters were placed. A pressurized reservoir of artificial CSF was connected by a three-way stopcock to the ventricular catheter so that ICP could be raised by intraventricular infusion of CSF. The composition of artificial CSF (in mM) was: Na⁺ 151, K⁺ 3, Ca²⁺ 1.25, Mg²⁺ 0.6, Cl⁻ 134, HCO₃⁻ 25, and urea 6. These concentrations are similar to those measured in lamb CSF (13). In control animals, the right jugular vein and carotid artery were isolated and ligated. In ECMO animals, the jugular vein catheter (14 French ECMO Venous Cannulae, Biomedicus Inc., Minneapolis, MN) was placed and advanced into the right atrium; the right carotid artery catheter (8–10 French, ECMO Arterial Cannulae, Biomedicus Inc.) was placed 3 cm above the aortic valve. This position was verified by pressure wave changes. All animals were systemically heparinized with 200 units/kg of heparin, followed by a heparin drip of 50–75 units/kg/h to maintain an activated clotting time of 200–250 s.

ECMO procedure. Venoarterial ECMO, as described before (12), was used for the study with the circuit consisting of the venous catheter, standard 1/4 × 1/4 inch polyvinyl chloride tubing, a 50-mL venous reservoir (R50, SciMed, Life Systems, Inc., Minneapolis, MN), a roller occlusion pump (Picker International, Mayfield Village, OH), a 0.8 m² SciMed membrane lung, a heat exchanger (P-7-14, SciMed), and the return arterial catheter. A flow of 120–150 mL/kg/min was used for the study.

Experimental protocol. After surgery, the animals were given pancuronium bromide (0.1 mg/kg) and pentobarbital (3 mg/kg/h) and were maintained on a constant infusion of 10% dextrose, 0.45% saline at 20–25 mL/kg/h. End-tidal CO₂ was monitored, and ventilation was adjusted to maintain PaCO₂ at approximately 4–7 kPa. PaO₂ was maintained at 13.3–26.7 kPa throughout the study period. Temperature was monitored and maintained at 39 ± 0.5°C.

After a 1-h stabilization period, animals were divided into two groups for the study: control animals ($n = 7$) with carotid artery and jugular vein ligation only, followed by a 1-h stabilization period after ligation (without ECMO); and ECMO animals ($n = 7$) placed on ECMO at 120 to 150 mL/kg/min for 1 h of stabilization. ECMO animals remained on ECMO during the autoregulation study period. In both groups, cerebral autoregulation was evaluated by increasing ICP and lowering CPP to achieve four ranges of CPP [CPP = MAP (mm Hg) – ICP]: 1) baseline (>50), 2) 55–40, 3) 39–25, and 4) <25 mm Hg. In each study group, ICP was increased over a 3- to 4-min period to achieve the desired level. Each ICP level was maintained for 5 min before studies were done. After the study, animals were euthanized with a pentobarbital overdose and KCl injection.

Physiologic measurements. CBF was measured by the radiolabeled microsphere technique (14). Radioactive microspheres of 15 ± 1.0 μM diameter (approximately 1.4 × 10⁸ microspheres) labeled with ¹⁵³Gd, ¹¹⁴In, ¹¹³Sn, ¹⁰³Ru, ⁹⁵Nb, and ⁴⁶Sc (New England Nuclear-Dupont Products, Boston, MA) were randomly chosen and 0.5 mL were injected over 45 s into the left ventricular catheter in the controls and into the arterial return catheter in ECMO animals. Previous studies have validated the injection of microspheres into the arterial catheter in ECMO animals (12). Ten s before the injection, a reference blood sample withdrawal was started from the lingual artery at a rate of 2.47 mL/min with a calibrated syringe pump (Harvard Apparatus, Dover, MA), and was continued for 60 s after the injection was complete. Tissue and reference blood samples were counted in a deep-well gamma scintillation counter (Packard Multichannel Autogamma Scintillation Spectrometer, model 9042, Packard Instrument Co., Inc., Downers Grove, IL). Blood flow was calculated as the product of tissue counts times the reference withdrawal rate divided by the counts in the reference blood sample. Flows were normalized to 100 g of tissue weight. Blood flows were determined for total cerebrum, right and left cerebral hemispheres, brainstem, caudate, cerebellum, and areas of flow for the middle

cerebral artery, posterior cerebral artery, anterior cerebral artery, and watershed area for the posterior-middle cerebral artery. All reference blood and tissue samples contained more than 400 microspheres.

Heart rate, MAP, ICP, CPP, arterial and venous pH, PCO₂, PO₂, Hb oxygen saturation, and Hb were measured at each study period. Samples for Hb oxygen saturation and Hb were taken immediately before the injection of the microspheres. Measurements were made using the Hemoximeter OSM2 (Radiometer, Cleveland, OH) calibrated for lamb's blood. PO₂, PCO₂, and pH were measured at 39.5°C using the Radiometer ABL 30. Blood pressure, sagittal sinus pressure, and ICP were continuously monitored (Gould Instruments, Ormand, CA).

Calculated values and data analysis. CMRO₂ was calculated by multiplying blood flow to hemispheres by the cerebral arteriovenous oxygen content difference [CMRO₂ = CBF × (cerebral arterial oxygen content – cerebral venous oxygen content)]. OT was calculated as the product of CBF times arterial oxygen content. E was calculated as the ratio of CMRO₂ to OT. Differences within group study variables were analyzed using repeated measures analysis of variance, with statistical significance defined as $p < 0.05$. Post hoc analysis of the significant differences was conducted using the Newman-Keuls test to determine points of significance. Between-group differences were determined using the two-tailed t test for independent variables with significance defined as $p < 0.05$.

RESULTS

The average weight (ECMO 4.3 ± 1, control 4.8 ± 1.5 kg) and age (ECMO 4.3 ± 1.6, control 4.4 ± 2.1 d) of the two groups did not vary significantly.

Physiologic variables are shown in Table 1. There were no changes in heart rate, MAP, pH, PaCO₂, PaO₂, arterial oxygen saturation, or pulse pressure over the study period in either group. ICP was increased over the study period to achieve the appropriate CPP in both groups. There were no differences in heart rate, pH, PaCO₂, arterial oxygen saturation, pulse pressure, CPP, or ICP between study groups. PaO₂ was significantly higher in the ECMO group due to the efficiency of the membrane lung ($p = 0.05$). MAP was lower in the ECMO animals at baseline (69 ± 19 versus 88 ± 19 mm Hg; $p = 0.04$). Because there were no differences between groups in CBF or CMRO₂ at these points, these differences are probably of little or no physiologic significance.

Cerebral autoregulatory curves for control and ECMO animals are shown in Figures 1 and 2. CBF decreased from baseline at CPP of 39–25 and <25 mm Hg in ECMO animals ($p < 0.001$) (Table 2). In controls, CBF decreased only at a CPP <25 mm Hg ($p < 0.03$). CBF was lower at CPP of 39–25 and <25 mm Hg in the ECMO animals when compared with controls ($p < 0.03$).

Cerebral metabolism measurements are shown in Table 3 for control and ECMO animals. OT decreased in the ECMO animals at CPP of 39–25 and <25 mm Hg when compared with baseline ($p < .001$) and in the controls at a CPP of <25 mm Hg ($p = 0.04$). OT was different between the ECMO and control groups at CPP of 55–40, 39–25, and <25 mm Hg ($p < 0.03$). Compared with baseline values, CMRO₂ was lower in the ECMO animals at CPP of 39–25 and <25 mm Hg ($p = 0.0002$), and in the control animals at a CPP <25 mm Hg, *i.e.* the point when autoregulation was lost in both groups. CMRO₂ in the ECMO animals was lower than that of the control animals at CPP of 39–25 and <25 mm Hg ($p < 0.02$). E did not change in the ECMO animals, but it increased at a CPP of <25 mm Hg in the control animals ($p = 0.03$).

The right to left cerebral hemisphere differences in the ECMO animals are shown in Figure 3. Although both hemispheres were different from baseline at CPP of 39–25 and <25 mm Hg, the right cerebral hemisphere showed a lower CBF than the left at

Table 1. Cardiovascular and blood gas values in ECMO and control animals as cerebral perfusion pressure was decreased*

	Baseline	CPP 55–40 mm Hg	CPP 39–25 mm Hg	CPP <25 mm Hg
Heart rate (bpm)				
ECMO	225 ± 32	229 ± 41	209 ± 49	214 ± 34
Control	237 ± 60	224 ± 66	234 ± 62	219 ± 66
Pulse pressure (mm Hg)				
ECMO	32 ± 13	32 ± 15	29 ± 10	36 ± 10
Control	39 ± 7	36 ± 5	36 ± 8	40 ± 9
MAP (mm Hg)				
ECMO	69 ± 19†	72 ± 23	71 ± 19	77 ± 16
Control	88 ± 12	82 ± 15	78 ± 17	79 ± 15
ICP (mm Hg)				
ECMO	4 ± 3	27 ± 34	42 ± 19	57 ± 18
Control	8 ± 3	34 ± 14	45 ± 15	58 ± 15
CPP (mm Hg)				
ECMO	66 ± 19	48 ± 6	30 ± 4	19 ± 3
Control	79 ± 15	48 ± 3	33 ± 4	20 ± 5
pH				
ECMO	7.36 ± 0.06	7.37 ± 0.05	7.38 ± 0.07	7.37 ± 0.07
Control	7.37 ± 0.03	7.35 ± 0.03	7.34 ± 0.03	7.33 ± 0.03
Paco ₂ (kPa)				
ECMO	4.5 ± 0.13	4.5 ± 0.27	4.4 ± 0.40	4.5 ± 0.40
Control	4.4 ± 0.40	4.5 ± 0.27	4.5 ± 0.27	4.4 ± 0.27
PaO ₂ (kPa)				
ECMO	16.3 ± 4.8	19.0 ± 4.8†	18.3 ± 4.0†	18.3 ± 4.0†
Control	14.3 ± 2.8	13.8 ± 2.8	13.8 ± 3.6	13.8 ± 3.6
SaO ₂				
ECMO	0.94 ± 0.06	0.97 ± 0.03	0.97 ± 0.03	0.96 ± 0.03
Control	0.94 ± 0.05	0.94 ± 0.04	0.93 ± 0.04	0.93 ± 0.04

* ECMO, $n = 7$; control, $n = 7$. Values displayed as mean ± SD. SaO₂, arterial oxygen saturation.

† $p < 0.05$ ECMO compared with control.

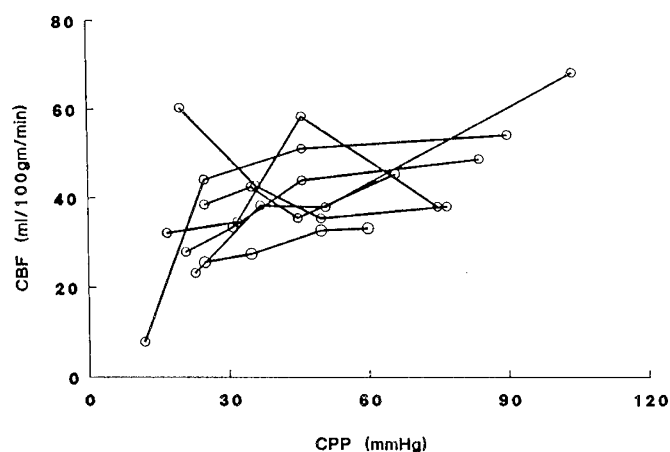


Fig. 1. Data from individual control animals ($n = 7$), depicted as changes in CBF in relationship to CPP.

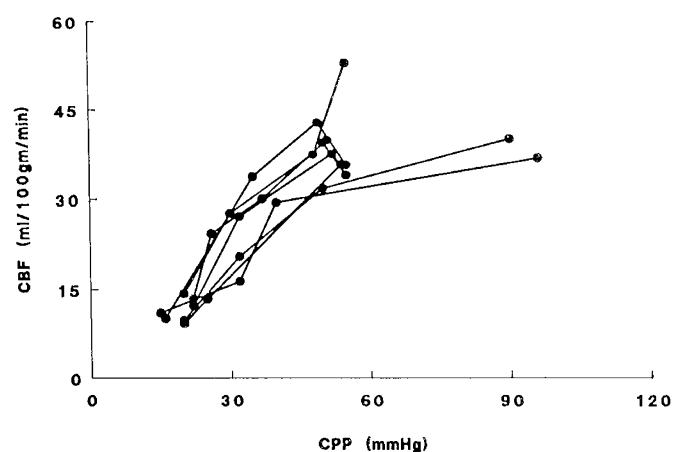


Fig. 2. Data from individual ECMO animals ($n = 7$), depicted as changes in CBF in relationship to CPP.

CPP of 39–25 and <25 mm Hg ($p < 0.005$). Right and left cerebral hemisphere flows of the ECMO animals were lower than those of the controls at CPP of 39–25 and <25 mm Hg ($p < 0.03$). Only the right hemisphere flows in the control animals decreased from baseline at a CPP of <25 mm Hg ($p = 0.03$) (Table 2).

Regional flow changes over CPP in both ECMO and control animals are shown in Table 2. The CBF changes in ECMO animals in all regions were the same except for the brainstem, where CBF decreased at CPP of 55–40, 39–25, and <25 mm Hg ($p < 0.01$). CBF differences between the ECMO and control animals in all regions were noted at CPP of 39–25 and <25 mm Hg ($p < 0.01$). Brainstem and posterior middle cerebral artery flows in control animals decreased at a CPP of <25 mm Hg ($p < 0.05$). Caudate flow decreased at CPP of 39–25 and <25 mm Hg ($p = 0.003$), whereas cerebellum, middle cerebral artery,

posterior cerebral artery, and anterior cerebral artery did not change from baseline at any CPP in the control animals.

DISCUSSION

Our data show that cerebral autoregulation is altered during venoarterial ECMO in healthy newborn lambs and that at the point of loss of cerebral autoregulation CMRO₂ is also decreased. Our data also show right-left CBF differences at the point of loss of cerebral autoregulation (CPP 39–25 in ECMO animals, CPP <25 mm Hg in the control animals). This finding suggests that vessel ligation is an added risk for cerebral injury when CBF is disrupted.

The significance of the findings in this study is that our model is one of normothermic partial CPB, allowing evaluation of the effect of bypass alone on cerebral autoregulation, without the confounding factors of hypothermia and acid-base blood gas

Table 2. Regional CBF (mL/100 g/min) for ECMO and control animals as cerebral perfusion pressure was decreased*

	Baseline	CPP 55-40 mm Hg	CPP 39-25 mm Hg	CPP <25 mm Hg
ECMO (n = 7)				
Total cerebrum	39 ± 7	35 ± 5	23 ± 7†‡	11 ± 2†‡
Right hemisphere	38 ± 6	33 ± 6	15 ± 12†‡§	3 ± 3†‡§
Left hemisphere	42 ± 7	37 ± 4	32 ± 4†‡	21 ± 2†‡
Brainstem	50 ± 8	44 ± 4†	33 ± 6†‡	18 ± 3†‡
Caudate	47 ± 5	40 ± 8	25 ± 10†‡	17 ± 13†‡
Cerebellum	65 ± 9	58 ± 14	39 ± 15†‡	16 ± 3†‡
MCA	41 ± 8	42 ± 9	25 ± 9†‡	13 ± 1†‡
ACA	38 ± 7	33 ± 6	25 ± 10†‡	12 ± 5†‡
PCA	37 ± 6	33 ± 2	23 ± 9†‡	9 ± 2†‡
PMCA	41 ± 9	36 ± 5	21 ± 10†‡	10 ± 4†‡
Control (n = 7)				
Total cerebrum	48 ± 10	42 ± 5	36 ± 7	27 ± 2†
Right hemisphere	43 ± 9	40 ± 9	34 ± 7	24 ± 18†
Left hemisphere	50 ± 14	44 ± 10	41 ± 7	34 ± 15
Brainstem	51 ± 9	52 ± 12	48 ± 9	36 ± 15†
Caudate	61 ± 12	51 ± 18	41 ± 6†	31 ± 14†
Cerebellum	71 ± 11	67 ± 14	62 ± 10	46 ± 28
MCA	47 ± 9	49 ± 15	46 ± 13	36 ± 23
ACA	42 ± 11	41 ± 7	42 ± 11	37 ± 34
PCA	46 ± 16	60 ± 44	60 ± 60	44 ± 43
PMCA	54 ± 16	45 ± 13	38 ± 8	31 ± 23†

* Values displayed as mean ± SD. MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; PMCA, posterior-middle artery watershed area.

† $p < 0.03$ compared with baseline.

‡ $p < 0.03$ comparing ECMO with control.

§ $p < 0.005$ comparing right hemisphere with left hemisphere.

Table 3. Cerebral metabolic measurements in ECMO and control animals as cerebral perfusion pressure was decreased*

	Baseline	CPP 55-40 mm Hg	CPP 39-25 mm Hg	CPP <25 mm Hg
CMRO ₂ (mL/100 g/min)				
ECMO	3.9 ± 1.1	3.7 ± 0.8	2.3 ± 0.9†‡	1.5 ± 0.9†‡
Control	4.2 ± 1.1	4.3 ± 1.2	4.0 ± 0.7	3.2 ± 1.3‡
E				
ECMO	0.55 ± 0.11	0.65 ± 0.14	0.65 ± 0.20	0.70 ± 0.15
Control	0.54 ± 0.09	0.62 ± 0.12	0.67 ± 0.14	0.75 ± 0.14‡
OT (mL/100 g/min)				
ECMO	6.4 ± 1.3†	5.8 ± 0.8†	3.4 ± 1.1†‡	2.0 ± 0.8†‡
Control	8.0 ± 2.5	6.9 ± 0.7	6.2 ± 1.4	4.8 ± 2.8‡

* ECMO, n = 7; control, n = 7. Values displayed as mean ± SD.

† $p < 0.03$, ECMO compared with control.

‡ $p < 0.04$ compared with baseline.

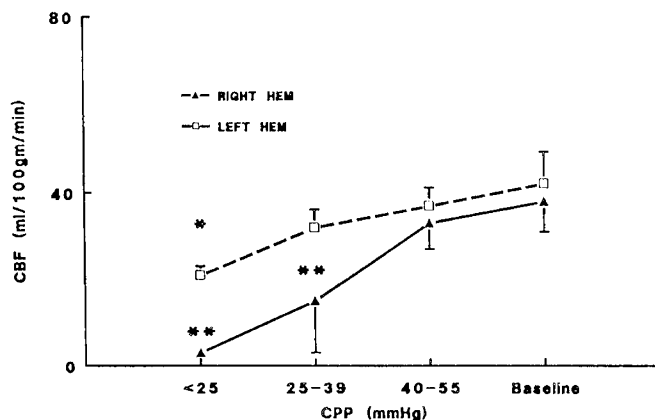


Fig. 3. Right and left hemisphere (HEM) CBF changes over the four CPP ranges for ECMO animals (n = 7). Data presented as mean ± SD. *, $p < 0.001$ compared with baseline values for each hemisphere; **, $p < 0.005$ comparing right with left hemisphere flows.

management seen in CPB studies. Results of human studies of the effect of CPB on cerebral autoregulation are conflicting, with some authors showing altered cerebral autoregulation (6, 7) and others showing no effect (8, 9). Besides differences in hypothermia, acid-base management, and other parameters such as anesthesia and membrane lung *versus* bubble oxygenators, all clinical studies have been limited in their ability to critically assess cerebral autoregulation because of the narrow range of blood pressures and CPP that can be studied (9). Review of most studies shows that the ranges of CPP or MAP are within the normal autoregulatory range. To demonstrate a shift in the autoregulatory threshold, CPP must be systematically varied over a wide range, which is difficult in clinical settings. The present study, through the use of an animal model that eliminates hypothermia and acid-base management as confounding factors, has clearly shown that partial normothermic bypass alters cerebral autoregulation. The lower limit of autoregulation in the ECMO animals was at a CPP of 39-25 mm Hg, whereas control animals autoregulated to a CPP <25 mm Hg. With the decrease in CBF at the point of loss of autoregulation, OT decreased and E did not increase to stabilize CMRO₂. These alterations in cerebral metabolism could result in cerebral injury if this state persists.

Autoregulation of the cerebral circulation was first observed by Fog in 1930 (15), with the concept of blood flow constancy during perfusion pressure changes fully established by Lassen in 1959 (16). The precise mechanism of autoregulation remains obscure, but two mechanisms have been suggested: Myogenic and metabolic (1–3). According to the myogenic hypothesis, the arterioles respond to intravascular pressure as a stimulus, with pressure elevation causing constriction. It could be postulated that the effect of altered pulsatile blood flow caused by the ECMO pump could effect cerebral autoregulation through the myogenic response. The effect of nonpulsatile flow on the brain has been of concern in CPB (17, 18). Tranmer *et al.* (18) compared pulsatile and nonpulsatile bypass in dogs with acute focal cerebral ischemia and found that pulsatile flow increased CBF significantly over nonpulsatile flow. In the present study, only partial CPB was used. Although systemic pulse pressures were not significantly changed by the ECMO flows used in this study, Doppler flow studies in infants on ECMO similar to those used in this study have shown that the anterior cerebral artery pulse pressures are dramatically altered (19). Thus, the effect of ECMO on the myogenic mechanisms of cerebral autoregulation could be responsible for the alteration seen in this study. This could be tested by studying a form of ECMO that allows normal cardiac output from the left ventricle, such as venovenous ECMO.

The metabolic hypothesis for cerebral autoregulation states that changes in micro-environment alter the vasomotor response, with vasoactive substances such as adenosine being implicated as mediators of the response (1–3). It is known that vasoactive mediators such as complement and prostaglandins are activated by exposure of blood to artificial surfaces in ECMO and CPB (20, 21). It could be postulated that an altered relationship of these vasoactive agents, *i.e.* increased production caused by contact with artificial surfaces, or an alteration of their metabolism could play a role in the alterations of cerebral autoregulation, but these hypotheses were not tested in this study. The effect of other potentially toxic substances such as plasticizers, which are known to come off the ECMO circuit tubing in significant amounts (22), on the brain is unknown but should be considered when addressing possible mechanisms of altered cerebral reactivity.

Altered autoregulation has been implicated in cerebral injury by making the cerebral microvasculature vulnerable to systemic blood pressure changes (23, 24). Although our findings of altered cerebral autoregulation are in healthy newborn lambs and may not be necessarily extrapolated to the sick, newborn human infant, they do raise concern for the effect of the ECMO procedure itself on cerebral autoregulation and could implicate the ECMO procedure as a risk factor for cerebral injury, which helps to explain the increased risk for intracranial abnormalities noted in the ECMO population (11). In the present study, CMRO₂ was significantly reduced when autoregulation was lost, indicating the potential for cerebral injury. Clinically, during the first hours of ECMO therapy, significant cardiovascular changes can occur, including hypertension and/or hypotension. Each of these events can result in significant changes in CPP and in the face of loss of cerebral autoregulation could cause either cerebral ischemia or hyperemia. Sell *et al.* (25) have reported a significant relationship between hypertension while on ECMO and the increased incidence of intracranial hemorrhage seen in their population. Infants placed on ECMO are also recovering from severe hypoxia and/or asphyxia, both of which are known to alter cerebral autoregulation (1, 3, 5).

Although right-sided cerebral lesions are not consistently found in the ECMO population, Schumacher *et al.* (26) noted a predominance of right-sided lesions in infants who were placed on ECMO during cardiopulmonary resuscitation (11). Increased vulnerability of the right side of the brain to changes in CBF with vessel ligation, combined with the added risk for cerebral ischemia from altered cerebral autoregulation secondary to the

ECMO procedure, as seen in our study, may explain the findings of Schumacher *et al.*

The limitations of our study are 3-fold: the acute nature of the preparation, the use of the newborn lamb, and the limited evaluation of the autoregulatory curve. Because only 1 h of ECMO exposure was used in this preparation, we did not address the long-term effect of ECMO on cerebral autoregulation; most infants are on ECMO for 5–6 d (10). It could be postulated that only the first few hours on ECMO are of concern because of the significant cardiovascular changes that occur during this time period. This would be supported if the etiology of these changes is solely due to activation of vasoactive mediators. Unfortunately, other possible etiologies, such as toxic substances (plasticizers), must be considered, and in such cases the exposure can be for days. Under these circumstances, the alterations in cerebral autoregulation could continue with time on ECMO.

The human circle of Willis receives blood from the internal carotid artery, whereas the circle of Willis in the lamb is supplied from the external carotid through a rete mirabile with no contribution from a vertebrobasilar connection (27, 28). If altered pulsatile flow was thought to be a mechanism in the changes seen in autoregulation, presence of the rete mirabile could raise theoretical concerns as to whether pulse pressure would be dampened with pulse pressure changes not being transmitted to the brain in this model. These concerns have been disproved by studies in the goat, which has the same vascular anatomy as the sheep, that have shown that pressure is pulsatile in the middle cerebral artery (29). Studies in our laboratory using transcranial Doppler techniques have shown normal pulse pressures in the small cerebral arteries of the lamb (30). Another concern is the well-developed vertebral-carotid anastomosis via the occipital artery in the lamb, which could mask the right-left CBF changes. Because right-left CBF changes were found in our study, this risk may be greater in the human, in whom this anastomosis is not as developed (28). The other anatomical concern in the lamb is the presence of a brachycephalic trunk off the aortic arch, from which the carotid arteries arise (31). Previous studies in our laboratory evaluating three simultaneous reference sites (left and right brachial arteries and lingual arteries) have shown that equal distribution of flow occurs with the ECMO arterial catheter in place, without evidence of obstruction (12).

Cerebral autoregulation is evaluated by changing CPP over a wide range. This can be evaluated in one of three ways: increasing or decreasing systemic pressure, increasing ICP, or elevating cerebral venous pressure (32, 33). Because of the mechanism on the ECMO system, called the "venous return monitor," which stops the ECMO pump if venous return is decreased (which would occur with graded hemorrhage), one cannot use the method of lowering systemic pressure for determining cerebral autoregulation. Therefore, the method used in this study was that of increasing ICP and thus lowering CPP, a method used extensively in physiologic research (32–35). The limitations of this method are that only the lower end of the autoregulatory curve can be determined, and thus we have not addressed the upper limits of autoregulation in this model.

In summary, we have shown that normothermic partial CPB or ECMO significantly alters cerebral autoregulation in the healthy newborn lamb and that carotid ligation with ECMO may be an important risk factor in right-sided cerebral ischemia when CBF autoregulation is lost. Although mechanisms for these findings are not understood, these findings do indicate that significant cardiovascular alterations, such as severe hypotension, could result in CBF alterations and, if prolonged, could result in cerebral injury. Although it is difficult to extrapolate these findings in the healthy, newborn lamb to the sick, human infant, one should consider that cerebral autoregulation alterations secondary to the ECMO procedure could be a risk factor for the development of cerebral injury in the sick newborn placed on ECMO.

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