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Jugular ligation does not increase intracranial pressure but does increase bihemispheric cerebral blood flow and metabolism

Paul J. Chai, MD; Lynne A. Skaryak, MD; Ross M. Ungerleider, MD; William J. Greeley, MD; Frank H. Kern, MD; Scott R. Schulman, MD; Doug R. Hansell, RRT; Richard L. Auten, MD; Samuel F. Mahaffey, MD; Jon N. Meliones, MD

Objectives: To answer the following questions: a) Does jugular venous ligation (simulating venovenous extracorporeal life support) alter proximal jugular venous pressure, intracranial pressure, hemispheric cerebral blood flow, or cerebral metabolism? b) Does release of ligation reverse these effects? and c) What are the comparative effects of venous ligation alone vs. venous ligation in combination with arterial ligation?

Design: Prospective, randomized, laboratory investigation.

Setting: Multidisciplinary laboratory setting.

Subjects: Sixteen swine, weighing 8.1 to 12.1 kg, 3 to 4 wks of age.

Interventions: Sixteen swine were randomly assigned to two groups, utilizing a random sequence of vessel ligation. Nine swine underwent occlusion of the right internal and external jugular veins alone (venovenous ligation) followed by release of the occlusion and then occlusion of the right common carotid artery and the right internal and external jugular veins together (venoarterial ligation). The remaining seven swine underwent venoarterial ligation, followed by release of the occlusion and then venovenous ligation. In the experimental group in which venovenous ligation was performed first, the 5, and 30-min release periods after ligation were taken to represent the effects of draining the right jugular vein during venovenous extracorporeal life support.

Measurements and Main Results: Data were obtained at baseline, 5, and 30 mins after each ligation/release period. Intracranial pressure, right and left internal jugular pressures/flow rates, and cerebral sinus lactate concentrations were measured. Cerebral blood flow was determined using ^{133}Xe clearance methodology, and the cerebral metabolic rate was calculated. There were no significant differences between the ipsilateral internal jugular pressure or extracorporeal life support at 5 or 30 mins after venovenous or venoarterial ligation compared with baseline values or compared with the release of the ligation at 5 or 30 mins. There was a significant increase in right-side (44.7 ± 2.0 vs. 38.8 ± 2.4 mL/kg/min; $p < .05$) and left-side (42.9 ± 2.3 vs. 38.7 ± 1.9 mL/kg/min; $p < .05$) cerebral blood flow 5 mins after venovenous ligation when compared with baseline values. Similarly, after venoarterial ligation, there was a significant increase in right-side (44.6 ± 2.2 vs. 38.8 ± 2.4 mL/kg/min; $p < .05$) and left-side (43.9 ± 1.5 vs. 38.7 ± 1.9 mL/kg/min; $p < .05$) cerebral blood flow. Cerebral oxygen consumption was significantly increased after venovenous (2.7 ± 0.2 to 3.2 ± 0.2 mL/kg/min; $p < .05$) and venoarterial (2.7 ± 0.2 to 3.1 ± 0.2 mL/kg/min; $p < .05$) ligation at 5 mins after ligation. This increase persisted at the 30-min period and after release of ligation.

Conclusions: Ligation of the right jugular veins alone (venovenous ligation) or jugular veins and right carotid artery (venoarterial ligation) does not increase jugular venous pressures or intracranial pressure. However, this procedure does increase cerebral blood

From the Departments of Anesthesia (Drs. Greeley, Kern, and Schulman), Pediatrics (Drs. Hansell, Auten, and Meliones), and Surgery (Drs. Chai, Skaryak, Ungerleider, and Mahaffey), Duke Children's Hospital, Duke University Medical Center, Durham, NC.

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flow and cerebral oxygen consumption. These findings demonstrate that there is adequate decompression of the venous system by the cerebrovascular system and retrograde decompression during extracorporeal life support appears unwarranted. (Crit Care Med 1995; 23:1864–1871)

KEY WORDS: **extracorporeal membrane oxygenation; cerebral blood flow; intracranial pressure; critical care; hemodynamics; life-support systems; cerebral hemorrhage; central nervous system; brain; vasculature**

Extracorporeal life support has been utilized successfully to support neonates with several forms of severe respiratory failure (1, 2). The initial surgical approach for neonatal extracorporeal life support required cannulation of the right internal jugular vein and right common carotid artery (venoarterial bypass), which, in most instances, resulted in permanent ligation of the common carotid artery (1). A prominent risk of extracorporeal life support is central nervous system morbidity (including intracranial hemorrhage, which occurs in ~15% of neonates). The etiology of the hemorrhage remains unclear, although multiple factors including interruption of the right common carotid artery blood flow have been implicated. Early experience with venovenous extracorporeal life support, using a 14-Fr, dual-lumen cannula in neonatal patients, has shown that adequate support can be provided by this technique (3–5). However, the placement of a large venovenous cannula might limit central nervous system venous drainage and increase proximal jugular venous pressure and intracerebral pressure. This situation can result in a reduction of the cerebral arterial-venous pressure gradient, a reduction in cerebral blood flow, and predispose the infant to intracranial hemorrhage. Secondary to these concerns, several groups (6, 7) have recommended the placement of catheters retrograde into the internal jugular vein to "decompress" the presumed venous stasis that occurs. The purpose of this study was to evaluate the response of intracranial dynamics and the cerebral circulation to jugular ligation, with and without carotid ligation as is established during extracorporeal life support.

The central nervous system, however, has multiple interconnecting vessels, including the circle of Willis, vertebral vessels, and the left internal jugular vein, which may provide for adequate cerebrovascular decompression despite total or near total obstruction of the right internal jugular vein and/or right common carotid artery (8). We therefore hypothesized that ligation of the right jugular vein would not increase jugular venous pressures or increase intracranial pressure, even if the carotid artery inflow to a cerebral hemisphere was left intact. To test these hypotheses, we designed a randomized laboratory experiment to answer the following questions: a) Does venous ligation alone, in the absence of extracorporeal life support, alter jugular venous pressure, intracranial pressure, hemispheric cerebral blood flow, or cerebral metabolic rate? b) Does release of the ligation, analogous to retrograde cannulation with "shunting," reverse these effects? and c) How does cerebrovascular physiology differ when venous ligation alone is compared with venous ligation in combination with arterial ligation?

MATERIALS AND METHODS

This study was approved by Duke University's Animal Care and Use Committee. Care and use of all experimental animals were in accordance with the National Institutes of Health guidelines.

Animal Preparation. In 16 swine, anesthesia was induced by ketamine. The swine were then paralyzed with pancuronium and intubated. The ketamine was discontinued and anesthesia was maintained by a continuous intravenous fentanyl infusion, which was titrated to maintain a constant heart rate. A burr hole was placed in the sagittal suture of the cranium to allow sampling of sagittal sinus blood. A second burr hole was placed in the cranium just lateral to the sagittal suture for the placement of an intraparenchymal pressure catheter (Camino Laboratories, San Diego, CA) (Fig. 1, *top*). A catheter was placed in the femoral artery to monitor continuous mean arterial pressure and obtain arterial blood gas samples.

After median sternotomy was performed, the left atrium was catheterized. Bilateral neck dissections were performed for ligation of the right common carotid artery, right external and internal jugular veins, and monitoring of the left internal jugular vein blood flow (Fig. 1, *bottom*). A 24-gauge catheter was placed in each internal jugular vein for continuous measurement of intravascular venous pressure. Transonic flow probes (Transonic Systems, Ithaca, NY) were placed around each internal jugular vein. Heparin was then administered to the swine so that thrombosis would not occur during temporary vascular occlusion.

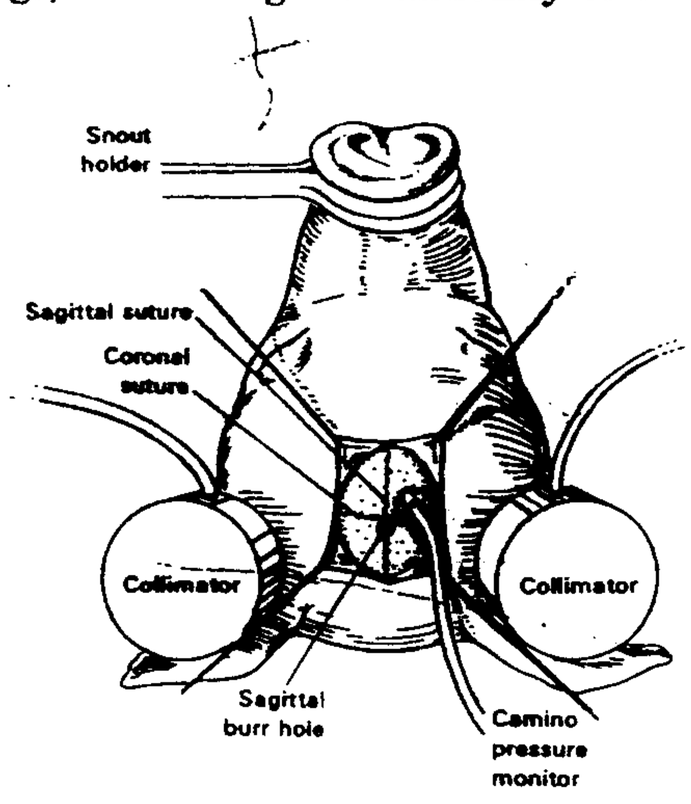
The goal of this study was to evaluate the effects of vessel ligation on cerebrovascular physiology,

independent of the effects of extracorporeal life support and hypoxia. Extracorporeal life support and hypoxia have been shown to cause alterations in central nervous system function (9). To separate the independent effects of vessel ligation from the effects of extracorporeal life support and hypoxia on central nervous system function, we performed simulated vessel ligation without the institution of extracorporeal life support or hypoxia. Simulation of venovenous ligation was performed by ligation of the right internal and external jugular vein only. Simulation of venoarterial ligation was performed by ligation of the right internal and external veins and the right common carotid artery.

Interventions. The 16 swine, 3 to 4 wks of age (8.1 to 12.1 kg), were assigned randomly to two groups, utilizing a random sequence of vessel ligation (Fig. 2). Nine swine underwent occlusion of the right external and internal jugular veins alone (venovenous ligation), followed by release of the occlusion and then occlusion of the right common carotid artery and right external and internal jugular veins together (venoarterial ligation) (Fig. 2). The remaining seven swine underwent venoarterial ligation, followed by release of the occlusion and then venovenous ligation. Each animal underwent 30 mins of vessel ligation (either venovenous ligation or venoarterial ligation), 30 mins of ligation release, and 30 mins of the other form of vessel ligation (Fig. 2).

In the experimental group in which venovenous ligation was performed first, the 5- and 30-min release periods after ligation were taken to represent the effects of draining the right jugular veins during venovenous extracorporeal life support. The release period after venoarterial ligation was not studied.

Measurements. Data were obtained at baseline and at 5 and 30 mins after each ligation/release period. Intracranial pressure (measured directly using the Camino V420 (Camino Laboratories) system hemodynamic data, right and left internal jugular pressures and flows (Transonic flow probes), and sagittal sinus lactate concentrations were measured at each data point. Hemispheric cerebral blood flow was determined at each measurement period using ^{133}Xe clearance methodology as has been previously described and used extensively by



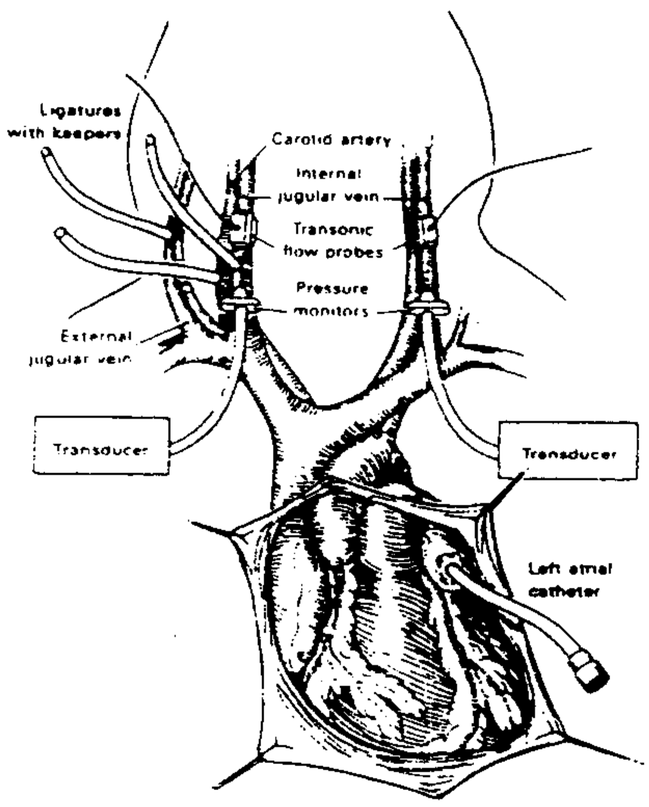


Figure 1. Schematic representation of the animal preparation. *Top:* Two burr holes are performed to facilitate placement of sampling and measuring devices. Collimators are placed to measure cerebral blood flow. *Bottom:* Ligatures with keepers are placed around the right internal and external veins and right carotid artery as indicated. Transducers and flow probes are also placed.

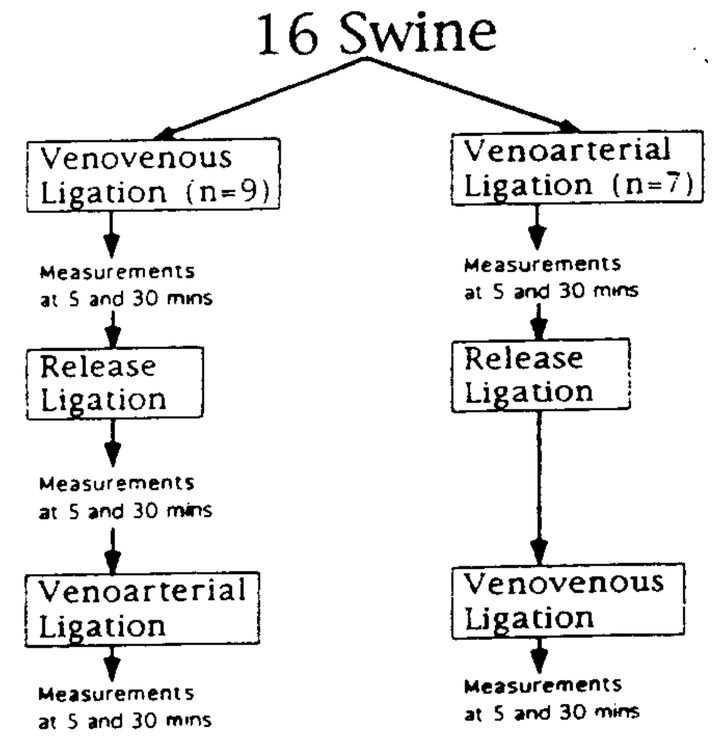


Figure 2. Sixteen swine were assigned randomly to one of the two treatment groups. The treatment sequences are as outlined. In one group, venovenous ligation was simulated by occlusion of the right internal and external jugular veins. In the other group, venoarterial ligation was simulated by complete occlusion of the right internal carotid artery and right internal jugular and external jugular veins.

ar group (10, 11). Cerebral oxygen consumption was calculated from the cerebral blood flow and measured arterial and sagittal sinus oxygen saturations. Arterial blood gases were held constant (Pao_2 >100 torr [>13.3 kPa], pH 7.35 to 7.45, $Paco_2$ 35 to 45 torr [4.7 to 6.0 kPa]) during the data collection period. All blood gases were analyzed using a blood gas monitor (Gem-Stat™, Mallinckrodt, Ann Arbor, MI). Hemoglobin and oxygen saturations were measured using a cooximeter (482, Instrumentation Laboratories, Lexington, MA).

Statistical Analysis. All data were obtained during a stable cardiorespiratory state, which was defined as a heart rate ±5% of baseline. Analysis of variance was used for statistical evaluation, with correction for repeated measures with a $p < .05$ interpreted to be statistically significant. All data are presented as mean ± SD.

RESULTS

There were no significant differences in arterial blood gases or mean arterial pressure at any measurement period.

Venovenous Ligation. The data are summarized in Table 1. After venovenous ligation, there was no significant difference between the right internal jugular vein pressure at 5 mins (3.9 ± 0.6 mm Hg) or 30 mins (4.6 ± 0.6 mm Hg) after ligation, compared with baseline values (4.0 ± 0.3 mm Hg) or compared with measurements made at 5 mins (3.7 ± 0.4 mm Hg) or 30 mins (3.9 ± 0.3 mm Hg) after release of the ligation (Fig. 3). The intracranial pressure also did not increase 5 or 30 mins after vessel ligation compared with baseline or after release of the ligation (Fig. 3). The left internal jugular vein demonstrated no significant change in pressure or flow with venovenous ligation or after release of the ligation.

Cerebral blood flow and cerebral oxygen consumption were significantly altered. Five minutes after venovenous ligation, there was a significant increase in right-side cerebral blood flow compared with baseline (44.7 ± 2.0 vs. 38.8 ± 2.4 mL/kg/min; $p < .05$) (Fig. 4). This increase in right-side cerebral blood flow persisted 30 mins after venovenous ligation and did not return to baseline after release of the ligation. Left-side cerebral blood flow was similarly increased after venovenous ligation (Table 1). Cerebral oxygen consumption was significantly increased 5 mins after venovenous ligation (2.7 ± 0.2 to 3.2 ± 0.2 mL/kg/min; $p < .05$). This increase in cerebral oxygen consumption persisted at 30 mins of ligation and after release of the ligation. There was a significant increase in sagittal sinus lactate concentration after venovenous ligation that persisted after release of the ligation (Table 1).

Venoarterial Ligation. After venoarterial ligation, there was no significant difference between the right internal jugular pressure at 5 mins (4.2 ± 0.4 mm Hg) or 30 mins (4.6 ± 0.5 mm Hg) after

Table 1. Results (mean ± SD)

		VV Ligation		Release Ligation		VA Ligation	
	Baseline	5 Mins	30 Mins	5 Mins	30 Mins	5 Mins	30 Mins
RIJ pressure (mm Hg)	4.0 ± 0.3	3.9 ± 0.6	4.6 ± 0.6	3.7 ± 0.4	3.9 ± 0.3	4.2 ± 0.4	4.6 ± 0.5
LIJ pressure (mm Hg)	5.1 ± 0.3	4.6 ± 0.5	4.8 ± 0.4	4.4 ± 0.5	4.8 ± 0.4	5.2 ± 0.4	5.1 ± 0.5
LIJF (mL/kg/min)	11.6 ± 2.2	9.9 ± 2.5	8.8 ± 2.4	7.9 ± 1.9	8.8 ± 2.2	11.8 ± 2.8	9.8 ± 2.3
ICP (mm Hg)	7.4 ± 0.7	7.6 ± 1.3	7.2 ± 1.0	6.0 ± 0.7	7.0 ± 0.8	6.6 ± 0.7	6.0 ± 0.4
CBF-R (mL/kg/min)	38.8 ± 2.4	44.7 ± 2.0[a]	43.9 ± 2.6[a]	44.6 ± 2.2[a]	45.8 ± 2.8[a]	47.0 ± 1.2[a]	42.9 ± 1.7[a]
CBF-L (mL/kg/min)	38.7 ± 1.9	42.9 ± 2.3[a]	43.1 ± 2.5[a]	43.9 ± 1.5[a]	42.6 ± 2.0[a]	46.2 ± 2.3[a]	42.8 ± 2.1[a]
$CMRO_2$ (mL/kg/min)	2.7 ± 0.2	3.2 ± 0.2[a]	3.2 ± 0.2[a]	3.2 ± 0.2[a]	3.1 ± 0.2[a]	3.1 ± 0.2[a]	3.0 ± 0.2[a]
MAP (mm Hg)	79.1 ± 3.9	70.4 ± 7.9	69.6 ± 7.9	71.6 ± 7.8	72.1 ± 7.9	86.3 ± 8.4	75.1 ± 7.5
Lactate (mmoL/L)	2.9 ± 0.3	3.5 ± 0.4[b]	3.9 ± 0.5[a]	3.5 ± 0.4[a]	3.6 ± 0.5[a]	3.6 ± 0.5[a]	3.7 ± 0.6[a]

VV, venovenous; VA, venoarterial; RIJ, right internal jugular; LIJ, left internal jugular; LIJF, left internal jugular flow; ICP, intracranial pressure; CBF-R, right hemisphere cerebral blood flow; CBF-L, left hemisphere cerebral blood flow; $CMRO_2$, cerebral metabolic rate; MAP, mean arterial pressure.

[a] $p < .05$ vs. baseline; [b] $p = .07$.

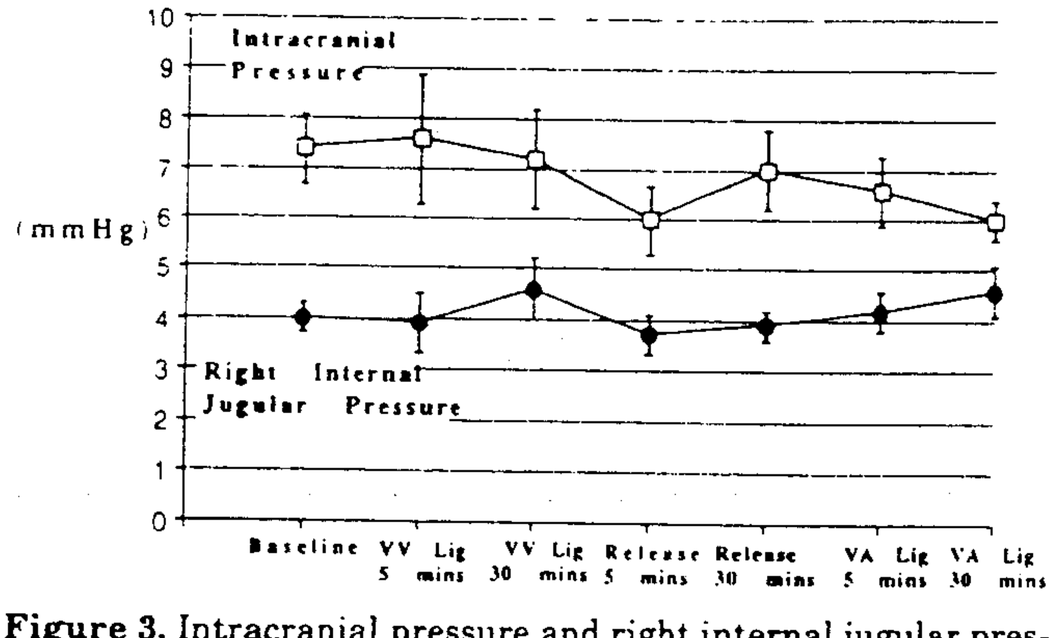


Figure 3. Intracranial pressure and right internal jugular pressure after the various interventions. There were no differences between the intracranial pressure or right internal jugular pressure measurements made at baseline after any intervention. Data are presented as mean ± SD. *VV Lig*, venovenous ligation; *VA Lig*, venoarterial ligation.

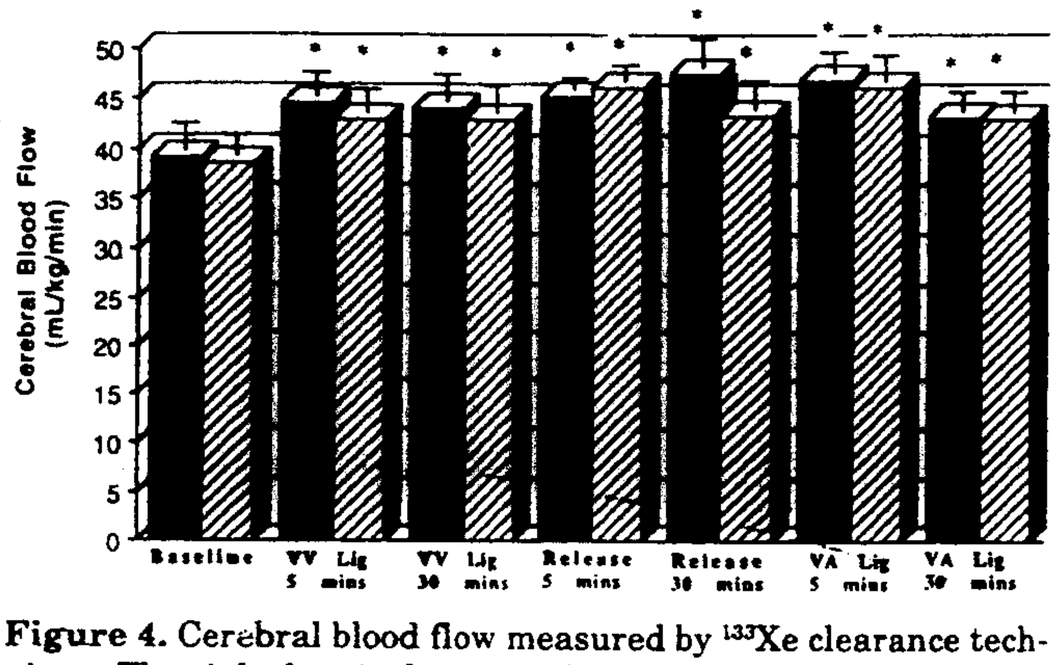


Figure 4. Cerebral blood flow measured by ^{133}Xe clearance technique. The right hemispheric cerebral blood flow is represented by the *solid bars*; the left cerebral blood flow is represented by the *hatched bars*. There was a significant increase in both right and left hemispheric cerebral blood flow after vessel ligation. Data are presented as mean ± SD. $^*p < .05$ vs. baseline. *VV Lig*, venovenous ligation; *VA Lig*, venoarterial ligation.

ligation when compared with baseline values (4.0 ±).3 mm Hg). The intracranial pressure also did not change 5 or 30 mins after venoarterial ligation compared with baseline (Fig. 3). There was no significant change in left internal jugular vein pressure or flow when venoarterial ligation was performed.

After venoarterial ligation, there was a significant increase in both right- and left-side cerebral blood flow at 5 and 30 mins after ligation compared with baseline (Fig. 4). However, no significant differences were noted when right- and left-side cerebral blood flow rates were compared during venoarterial ligation. Cerebral oxygen consumption was significantly increased 5 mins after venoarterial ligation (2.7 ± 0.2 to 3.1 ± 0.2 mL/kg/min; $p < .05$) and this increase persisted 30 mins after ligation. There was a significant increase in sagittal sinus lactate concentration after venoarterial ligation (Table 1).

Venovenous vs. Venoarterial Ligation. There were no significant differences when measurements made during venovenous ligation were compared with measurements made during venoarterial ligation.

DISCUSSION

This study was designed to examine the effects of jugular venous and carotid artery ligation on cerebrovascular physiology and metabolism. We evaluated the effects of vessel ligation alone, without the confounding variables of alterations in flow that might occur with various forms of extracorporeal life support and without the overlay of systemic hypoxemia and prolonged acidosis that frequently occurs in patients who begin receiving extracorporeal life support.

The relevance of this study is underscored by the controversies that have arisen regarding neurologic outcome after extracorporeal life support management. Although the survival rate after venoarterial extracorporeal life support management has been 80% or better in most series, there remains a 15% to 17% frequency of long-term neurologic dysfunction in these survivors. Several studies (9, 12) have demonstrated an increased frequency of right-side central nervous system lesions in extracorporeal life support patients when compared with controls. Concerns regarding the neurologic sequelae after ligation of the carotid artery, even if the artery is repaired after discontinuation of extracorporeal life support, have increased the enthusiasm for venovenous extracorporeal life support, which spares ligation of the carotid artery. Venovenous extracorporeal life support differs from venoarterial extracorporeal life support in several technical and physiologic principles. Unlike venoarterial extracorporeal life support, which requires cannulation and subsequent ligation of the right common carotid artery, neonatal venovenous extracorporeal life support can be accomplished through cannulation of the right internal jugular vein with a dual-lumen cannula that provides both arterial infusion and venous drainage. The overall survival rate after venovenous extracorporeal life support is slightly better (90%) than venoarterial extracorporeal life support, but this difference may reflect the fact that venovenous extracorporeal life support is not always considered or offered to patients with the highest mortality risk (e.g., neonates with severe hemodynamic instability). Despite the theoretical benefits of venovenous extracorporeal life support, there is no

mentation that the neurologic outcome after venovenous extracorporeal life support is superior to that outcome seen after venoarterial extracorporeal life support.

Although a great deal of information has been generated in recent years regarding the effect of conventional cardiopulmonary bypass (venoarterial) on cerebrovascular physiology and metabolism in neonates, very little attention has been given to the cerebrovascular effects of vessel ligation alone (10, 11, 13). Central questions to be asked include the following: a) What are the cerebrovascular effects of jugular vein ligation (venovenous ligation)? and b) Do these effects differ after simultaneous right carotid artery and right internal jugular vein ligation (venoarterial ligation)?

Venovenous Ligation. Ligation of the jugular vein an animal with normal hemodynamics should produce circulatory physiology that is similar to the c ılatory physiology that occurs during venovenous extracorporeal life support, since pulsatile flow is maintained during both approaches and cerebral blood flow is determined by similar physiologic stimuli (14). Of greatest concern is whether intravascular and/or intracerebral pressures increase when the arterial perfusion to the cerebral hemisphere is preserved while venous drainage is obstructed. Our data demonstrate that neither intravascular nor intracranial pressure is increased by venous ligation. The fact that venous ligation does not result in a significant increase in venous or cerebral parenchymal pressure suggests that the ipsilateral brain accommodates the arterial inflow and is adequately decompressed through the vertebral veins and the left jugular veins. These findings are not surprising and are consistent with what is ıown about the physiology of venous drainage. The venous system in most portions of the body can a ı to obstructions with little change in pressure, even when obstructions are acutely imposed. These findings suggest that there is no physiologic rationale for draining the jugular vein proximal to jugular ligation in patients cannulated for venovenous extracorporeal life support. This action only adds complexity and a source for complication to the circuit, without producing a physiologic advantage.

Cerebral blood flow, cerebral oxygen consumption, and cerebral lactate production are increased after venous and arterial ligation, despite no change in cerebral hemodynamics. The mechanism for these increases is not clear, although an increase in cerebral blood flow has previously been observed after cannulation and initiation of venoarterial extracorporeal life support (13, 15). It is likely that ligation of the right jugular vein or artery creates an acute decrease in global or regional cerebral oxygen delivery by alternating intracerebral blood flow patterns. Cerebral blood flow may then increase in an attempt to compensate for the imbalance between cerebral oxygen supply and demand.

The cerebral blood flow measured is a representation of global events and does not examine regional differences. Regional alterations in cerebral blood flow may help explain the physiologic derangements that occur after vessel ligation. Regional cerebral blood flow may be impaired after vessel ligation and result in a persistent imbalance between tissue oxygen supply and demand, despite adequate global cerebral blood flow. Inadequacy of regional oxygen delivery could result in an oxygen debt in the brain, stimulating an increase in cerebral blood flow until the oxygen debt is paid.

The persistent increase in cerebral oxygen consumption noted in this study after both venovenous or venoarterial ligation indicates increased metabolic activity of the brain. A significant and persistent increase in cerebral oxygen consumption would also explain the increase in cerebral blood flow, since cerebral blood flow is predominantly determined by alterations in cerebral metabolism (16). The etiology for the increased metabolism after vessel ligation is unknown. Cerebral oxygen consumption increased, while $Paco_2$, Pao_2, hematocrit, intracranial pressure, and mean arterial pressure did not change. Despite the increase in cerebral blood flow, cerebral lactate concentration also remained increased. Therefore, despite an increase in global cerebral blood flow and cerebral oxygen delivery, the oxygen demands in some region of the brain are not met, and a persistent inadequacy of regional oxygen delivery remains. Abnormalities in regional oxygen delivery, as a result of vessel ligation, may be the primary inciting event for cerebral injury, with increased cerebral oxygen consumption, lactate concentration, and cerebral blood flow occurring in response to these abnormalities. The etiology for the alterations in oxygen delivery and the exact mechanism that causes the increase in cerebral blood flow and cerebral oxygen consumption await further investigation. Release of the jugular ligation offered no benefit in resolving the increase in cerebral blood flow and metabolism that occurred, indicating that the abnormalities that develop would not be reversed by retrograde drainage.

Venoarterial Ligation. Doppler flow studies (15–18) from the carotid artery have demonstrated that arterial flow distal to the carotid ligation occurs almost immediately after ligation. In several

studies (17, 18), patients who underwent right internal jugular vein and right common carotid artery ligation during extracorporeal life support (venoarterial extracorporeal life support) maintained cerebral perfusion to the ipsilateral side. Although some investigators (13) have documented an initial decrease in hemispheric blood flow distal to carotid artery ligation in patients receiving venoarterial extracorporeal life support, the difference in hemispheric blood flow is reversed within hours, such that there are essentially no differences between hemispheric blood flow after the initiation of extracorporeal life support. In this study, venoarterial ligation resulted in an increase in cerebral blood flow and cerebral oxygen consumption that is similar to those increases demonstrated during venovenous vessel ligation. The differences between our findings and previous findings can be explained by the fact that the animals in this study did not receive extracorporeal life support after vessel ligation and were not hypoxic, and therefore would have intact cerebral autoregulation. In our study, swine had normal cardiovascular physiology and maintained pulsatile perfusion to the brain via the contralateral carotid artery.

In both our venoarterial and the venovenous ligation model, the right internal and external jugular veins were ligated. It is possible that the increase in cerebral blood flow and metabolism is related to venous ligation, irrespective of whether the carotid artery is occluded. In a previous study (19) in swine, right common carotid artery ligation alone produced no alterations in cerebral blood flow. That finding coupled with our data implicates venous ligation as the causative factor that alters cerebrovascular physiology. How this alteration occurs is unclear, since proximal jugular venous pressures remain normal. Possible explanations include regional alterations in interstitial or capillary hydrostatic pressure or capillary perfusion patterns. Short et al. (20) demonstrated an impairment in cerebral autoregulation with vessel ligation in a hypoxic system resulting in alterations in cerebral blood flow and cerebral oxygen consumption. The relatively smaller increase in cerebral blood flow (15%) seen in our study may be due to an incomplete compensatory response secondary to an impairment in cerebral autoregulation, as observed by Short et al (20).

What is apparent from this study, as well as from previous studies that have examined vessel ligation and extracorporeal life support, is that venoarterial ligation will not result in serious decrement of cerebral blood flow to the ipsilateral side. Of greatest interest is the similarity between the physiologic consequences of venoarterial and venovenous ligation, suggesting that there is no benefit to venovenous ligation vs. venoarterial ligation on the basis of cerebral perfusion.

Limitations. There are several limitations to this study that are related to the use of an animal model, the experimental design, and the simulation of extracorporeal life support.

Model Justification. Swine were chosen as the laboratory species, since their cerebral circulation and microcirculation are similar in anatomy and physiologic response to humans (14). In addition, the swine model has been used extensively in our laboratory and in other laboratories that have examined the effects of cardiopulmonary bypass on central nervous system function (14, 19). Swine, however, may not be completely similar to newborns who require extracorporeal life support since swine have a well-developed circle of Willis. While inadequate collateral vessels or an immature circle of Willis may occur in newborns, ultrasound studies have demonstrated that the majority of neonates had adequate collateral vessels and would have similar physiology to our model. Using flow probes during temporary carotid artery occlusion, it was found that the major route of cerebral drainage in swine is through the internal jugular vein. In our experiment, we ligated both the right internal and external jugular veins to ensure completeness. Ligation was performed by placing a 0 silk ligature around the venous or arterial vessel using a snare. This model is appropriate, since ligation was confirmed when flow distal to the snare was zero, which simulated complete ligation. The snare approach allowed for a return to baseline conditions after release of the snare. After release of the snare, the flow in the vessel returned to baseline and therefore measurements taken after release of the snare accurately represent what would occur with appropriate decompression by retrograde cannulation. Despite the limitations of the swine model, it is likely that the data reflect what occurs in the majority of newborns.

The time periods for evaluation were 5 and 30 mins. The 5-min period was performed to evaluate the acute effects of vessel ligation. The 30-min period after surgical manipulation was chosen to represent a steady-state measurement. It is possible that stabilization after surgical manipulation requires a longer time period than 30 mins and that the results would be different if the measurements were made at $\geq$1 hr after ligation. These evaluations were not performed since it would add extensive

time to the study and 30 mins after an intervention represents a clinically relevant period during which the central nervous system may be acutely susceptible to injury.

This study was designed to isolate and evaluate only one aspect of conventional extracorporeal life support, the effect of right jugular vein and/or right common carotid artery ligation on global cerebrovascular physiology and metabolism. This model was not designed to replicate the complexity of the various problems that are encountered and interact with one another in patients requiring extracorporeal life support.

This study investigated the effects of vessel ligation alone, as performed for patients requiring extracorporeal life support, separate from the confounding variables produced by models that replicate the other features of extracorporeal life support. The data from this study enable specific observations to be made regarding the effect of vessel ligation on cerebrovascular physiology and might be helpful in understanding outcomes observed after either venoarterial or venovenous extracorporeal life support. In particular, it is difficult to point to the ligation of a carotid artery as a causative factor in poor neurologic outcome, since the cerebral response from jugular vein ligation alone (without carotid ligation) is not measurably different or better. Likewise, there is no physiologic justification to warrant drainage of the jugular venous system cephalad to vessel ligation in patients exposed to either venoarterial or venovenous extracorporeal life support cannulation. Any differences in neurologic outcomes that can one day be attributed to venovenous vs. venoarterial extracorporeal life support will most likely be related to the other factors that distinguish these two techniques, and are not likely to be associated with which vessels are ligated, repaired, or drained.

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