

The Anesthetic Effects on Vasopressor Modulation of Cerebral Blood Flow in an Immature Swine Model

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BACKGROUND: The effect of various sedatives and anesthetics on vasopressor modulation of cerebral blood flow (CBF) in children is unclear. In adults, isoflurane has been described to decrease CBF to a lesser extent than fentanyl and midazolam. Most large-animal models of neurocritical care use inhaled anesthetics for anesthesia. Investigations involving modulations of CBF would have improved translatability within a model that more closely approximates the current practice in the pediatric intensive care unit.

METHODS: Fifteen 4-week-old piglets were given 1 of 2 anesthetic protocols: total IV anesthesia (TIVA) (midazolam 1 mg/kg/h and fentanyl 100 µg/kg/h, $n = 8$) or ISO (isoflurane 1.5%–2% and fentanyl 100 µg/kg/h, $n = 7$). Mean arterial blood pressure, intracranial pressure (ICP), CBF, and brain tissue oxygen tension were measured continuously as piglets were exposed to escalating doses of arginine vasopressin, norepinephrine (NE), and phenylephrine (PE).

RESULTS: Baseline CBF was similar in the 2 groups (ISO 38 ± 10 vs TIVA 35 ± 26 mL/100 g/min) despite lower baseline cerebral perfusion pressure in the ISO group (45 ± 11 vs 71 ± 11 mm Hg; $P < 0.0005$). Piglets in the ISO group displayed increases in ICP with PE and NE (11 ± 4 vs 16 ± 4 mm Hg and 11 ± 8 vs 18 ± 5 mm Hg; $P < 0.05$), but in the TIVA group, only exposure to PE resulted in increases in ICP when comparing maximal dose values with baseline data (11 ± 4 vs 15 ± 5 mm Hg; $P < 0.05$). Normalized CBF displayed statistically significant increases regarding anesthetic group and vasopressor dose when piglets were exposed to NE and PE ($P < 0.05$), suggesting an impairment of autoregulation within ISO, but not TIVA.

CONCLUSION: The vasopressor effect on CBF was limited when using a narcotic-benzodiazepine-based anesthetic protocol compared with volatile anesthetics, consistent with a preservation of autoregulation. Selection of anesthetic drugs is critical to investigate mechanisms of cerebrovascular hemodynamics, and in translating critical care investigations between the laboratory and bedside. (Anesth Analg 2013;116:838–44)

Traumatic brain injury (TBI) and stroke are common clinical conditions requiring admission to the intensive care unit, and are not uniquely adult diagnoses; both are in the top 10 causes of pediatric mortality.¹ Postinjury management tasks the practitioner to limit secondary injury from imbalances in brain tissue metabolic supply and demand, excitotoxicity, systemic hypotension/hypertension, and systemic hypoxemia. Adequate cerebral blood flow (CBF) is frequently targeted as a theoretical point of manipulation, with too little CBF associated with ischemic injury and too much CBF associated with increased cerebral blood volume, vasogenic edema, and

potential increases in intracranial pressure (ICP). Because CBF is difficult to measure on a continuous basis in the clinical setting, cerebral perfusion pressure (CPP) is often used as a surrogate. Although essential to the regulation of CBF, cerebrovascular resistance (CVR) regulation remains complex and poorly understood, even in the healthy brain. Regulation of CVR is heterogeneous and under local, not global control, with age and gender differences previously described.^{2–4} Furthermore, recent investigations have reported alterations in cerebrovascular function and physiology in critically ill patients without primary brain injury.^{5–8}

Whereas most IV sedative medications decrease cerebral metabolic rate (CMRO₂) and CBF in a proportional amount,⁹ the inhaled anesthetics have a more varied response. A study of adult patients undergoing elective neurosurgical procedures demonstrated a decrease in CBF of 37% while sedated with fentanyl and midazolam, compared with a 22% reduction when anesthetized with isoflurane (ISO), despite relative reductions of CMRO₂ of 26% and 51%, respectively.¹⁰ Additional studies have shown midazolam to be associated with as much a 71% decrease in CBF,^{9,11–15} although a single study did not see any difference in CBF with a midazolam infusion.¹⁶ Inhaled anesthetics such as ISO have been known to have more variable effects on CBF, ranging from a 22% decrease to a 33% increase at 1.0 minimal alveolar concentration.^{10,17–21} Unfortunately, only a small minority of these investigations have been performed

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in the pediatric population,¹⁹ and none were obtained in patients in the pediatric intensive care unit (PICU).

Vasopressors are frequently used in pediatric neurocritical care to modulate CPP, with the ultimate goal of increasing CBF. Phenylephrine (PE) is the most common vasopressor used in pediatric patients with TBI,²² because it selectively targets α receptors with pure systemic vasoconstriction. In mature-animal models, increases in ICP have been observed with PE administration.^{23,24} Norepinephrine (NE) activates α receptors for peripheral vasoconstriction, but has additional activation of β receptors for inotropy. It is gaining favor in adult neurocritical care as a preferred vasopressor, because it provides more predictable CPP augmentation compared with dopamine.^{24,25} Arginine vasopressin (AVP), with its novel targeting of the endothelial receptor V1, is often used in catecholamine refractory states.^{26,27} In adults with TBI, AVP is the fourth most frequently used vasopressor.²⁸ In swine TBI models, AVP was as effective as PE for CPP maintenance, but AVP was associated with lower ICP and higher brain tissue oxygen tension (PbtO₂).²⁹

The objectives of this study were twofold: (1) to develop an anesthetic paradigm for large-animal models that would improve the translatability of findings to the PICU. In animal models (both large and small), ISO is frequently used for anesthesia. It is our hope that using an animal model with an anesthetic paradigm clinically relevant to the PICU (in this case fentanyl and midazolam) will improve the chances of successfully translating new findings and therapies from the bench to the PICU bedside. (2) We believe there are several clinical scenarios in which vasopressors would be used in pediatric patients without intracranial pathology such as sepsis, trauma without head injury, and acute respiratory distress syndrome. Some of these pediatric critically ill patients may require operative intervention and during that intervention may be transitioned to volatile anesthetics from their IV infusions. Using an immature large-animal platform to model clinical practice in PICU patients requiring vasopressor therapy, we aimed to determine the cerebrovascular hemodynamic effects of different vasopressor drugs in piglets anesthetized with either fentanyl/midazolam or fentanyl/ISO.

METHODS

All procedures were approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania. Female, 4-week-old piglets (8–10 kg), which have been described to be anthropomorphically similar to a human toddler, were used for the study.³⁰ Piglets were premedicated with intramuscular injection of ketamine (20 mg/kg) and xylazine (2 mg/kg) followed by 4% ISO and 100% fraction of inspired oxygen via snout mask, until abolishment of reflexive withdrawal to a pinch stimulus. Endotracheal intubation was followed by decrease in fraction of inspired oxygen to 21% to 30%, and maintenance anesthesia was provided using 2% ISO. No neuromuscular blockade was administered for tracheal intubation or at any other point during the experiments. Two points of venous access were obtained via bilateral femoral cut-down. Additionally, the right femoral artery was cannulated for invasive blood pressure monitoring. Vital signs including heart rate, respiratory rate, mean arterial blood pressure (MAP) zeroed to the right

atrium, arterial oxygen saturation, end-tidal CO₂, and rectal temperature were recorded for the duration of the experiment. A 20 mL/kg normal saline bolus was administered for replacement of preanesthetic dehydration, followed by a normal saline infusion at 4 mL/kg/h. Mechanical ventilation was titrated with goals of normoxia (Pao₂ >90 mm Hg) and normocarbica (Paco₂ 38–45 mm Hg). The core body temperature goal of 37°C to 38.5°C was accomplished with a conductive warming/cooling blanket system (Gaymar, Orchard Park, NY). With piglets in the prone position, 3 bur holes were drilled for placement of intracranial monitors in the frontal lobes as previously described.³¹ ICP was monitored via a fiberoptic intraparenchymal pressure monitor (Integra, Plainsboro, NJ). PbtO₂ of the left frontal lobe subcortical white matter was monitored with a Licox monitor (Integra). CBF of the right frontal lobe subcortical white matter was measured continuously with a thermal diffusion intraparenchymal probe (Hemedex, Cambridge, MA).^{32,33}

After all instrumentation was completed, piglets were transitioned to 1 of 2 different anesthetic plans. The first group, total IV anesthesia (TIVA) ($n = 8$), had the ISO discontinued and flushed from the ventilator circuit. They were given a bolus of 1 mg/kg midazolam and 50 μ g/kg fentanyl and started on midazolam and fentanyl infusions (1 mg/kg/h and 100 μ g/kg/h, respectively).³⁴ The second group (ISO) ($n = 7$) was continued on ISO at 1.5% to 2% maintenance, given a fentanyl bolus (50 μ g/kg) followed by a fentanyl infusion (100 μ g/kg/h). The average latency between ketamine injection and baseline data procurement before first vasopressor was more than 2 hours; and between ISO discontinuation in TIVA and baseline data was more than 30 minutes with a gas flow rate of 5 L/min throughout the entire experiment.

Within each anesthetic group, each piglet was exposed to 3 vasopressors, AVP, NE, and PE, in random order, and doses were doubled every 15 minutes until 1 of 3 conditions was met to prevent injury or early death to the animals: (1) reaching the highest dose described in large-animal literature (AVP 0.08 U/kg/min,²⁶ NE 1.5 μ g/kg/min,³⁵ PE 25 μ g/kg/min²⁶); (2) significant bradycardia or tachycardia (>200 or <40 bpm); or (3) systolic blood pressure exceeded 145 mm Hg. Upon reaching any of these criteria, the vasopressor was discontinued, followed by a washout period exceeding 15 minutes, which was terminated when MAP values were stable for 5 minutes. Next, piglets were exposed to the second and subsequently third vasopressor in a similar manner. After termination of the third vasopressor, the piglet was euthanized via pentobarbital overdose.

Physiologic, arterial blood gas, and neuromonitoring variables data at baseline and at maximal vasopressor dose were analyzed within and across groups, using paired and unpaired Student *t* tests as appropriate. The MAP, CBF, and PbtO₂ data for each drug were compared across anesthetic groups and dose using repeated-measures analysis of variance (ANOVA) tests, and Tukey-Kramer tests were used for post hoc analysis with significance defined as $P < 0.05$.

RESULTS

Piglets in TIVA and ISO groups displayed similar baseline physiologic variables, except lower baseline MAP and CPP in the ISO group (Table 1). Although ICP was higher in the ISO group, it did not reach statistical significance ($P = 0.06$).

Table 1. Baseline Physiologic Data of Piglets

	TIVA	ISO
Weight (kg)	9.0 ± 1.0	8.2 ± 0.9
Rectal temperature (°C)	36.7 ± 0.6	36.7 ± 0.5
Heart rate (bpm)	111 ± 19	108 ± 17
Respiratory rate (breaths/min)	26 ± 3	27 ± 2
SaO ₂ (%)	98 ± 1	98 ± 1
MAP (mm Hg)	79 ± 10*	55 ± 10
ICP (mm Hg)	8 ± 3	11 ± 3
CPP (mm Hg)	71 ± 11*	45 ± 7
CBF (mL/100 g/min)	35 ± 27	38 ± 10
PbtO ₂ (mm Hg)	10.8 ± 4.3	13.5 ± 4.7
pH	7.53 ± 0.04	7.53 ± 0.02
Pco ₂	42.7 ± 3.1	40.0 ± 4.8
PaO ₂	137.0 ± 25.2	132.8 ± 25.4
Lactate	1.1 ± 0.3	1.6 ± 0.9

Values are mean ± SD. Baseline measurements were performed in each animal before exposure to vasopressor drug.

Total IV anesthesia (TIVA) = fentanyl and midazolam; ISO = fentanyl and isoflurane. SaO₂ = arterial oxygen saturation; MAP = mean arterial blood pressure; ICP = intracranial pressure; CPP = cerebral perfusion pressure; CBF = cerebral blood flow; PbtO₂ = brain tissue oxygen tension.

* $P < 0.001$

Table 2. Maximal Dose of Vasopressor at Which Termination Criteria Were Met

Vasopressor	TIVA	ISO
AVP (U/kg/min)	0.08 ± 0.03	0.06 ± 0.02
NE (µg/kg/min)	0.85 ± 0.44	0.54 ± 0.25
PE (µg/kg/min)	6.7 ± 2.9	4.5 ± 1.1

Values are mean ± SD.

Total IV anesthesia (TIVA) = fentanyl and midazolam; ISO = fentanyl and isoflurane. AVP = arginine vasopressin; NE = norepinephrine; PE = phenylephrine.

Table 3. Physiologic Response Comparing Characteristics at Vasopressor Initiation and Maximal Dose, Within TIVA and ISO Groups

	TIVA		ISO	
	Prevasopressor	Maximal dose	Prevasopressor	Maximal dose
AVP				
MAP (mm Hg)	73 ± 12*	90 ± 20†	54 ± 7	83 ± 21†
ICP (mm Hg)	12 ± 6	13 ± 4	14 ± 5	13 ± 7
CPP (mm Hg)	61 ± 13*	79 ± 19†	41 ± 4	70 ± 23†
PbtO ₂ (mm Hg)	15.6 ± 5.8	16.2 ± 6.8	16.1 ± 5.9	24.5 ± 11.6
CBF (mL/100 g/min)	38 ± 20	37 ± 25	33 ± 9	38 ± 20
Temperature (°C)	37.8 ± 0.2	37.5 ± 0.2	37.5 ± 0.2	37.8 ± 0.3
NE				
MAP (mm Hg)	77 ± 9*	90 ± 8†	55 ± 10	92 ± 14†
ICP (mm Hg)	14 ± 10	14 ± 4	11 ± 8	18 ± 5†
CPP (mm Hg)	63 ± 12*	75 ± 8	44 ± 14	74 ± 12†
PbtO ₂ (mm Hg)	16.1 ± 5.9	22.2 ± 5.9†	20.6 ± 9.9	36.3 ± 7.7††
CBF (mL/100 g/min)	30 ± 17	48 ± 15	29 ± 14	75 ± 22††
Temperature (°C)	37.9 ± 0.1	38.1 ± 0.2	37.8 ± 0.2	38.0 ± 0.1
PE				
MAP (mm Hg)	71 ± 11*	98 ± 23†	59 ± 8	114 ± 8†
ICP (mm Hg)	11 ± 4	15 ± 5†	11 ± 4	16 ± 4†
CPP (mm Hg)	60 ± 10	83 ± 20†	48 ± 10	98 ± 10†
PbtO ₂ (mm Hg)	11.3 ± 3.4*	18.8 ± 6.4†	20.1 ± 8.6	38.1 ± 9.5††
CBF (mL/100 g/min)	41 ± 24	41 ± 23	35 ± 14	77 ± 25††
Temperature (°C)	37.6 ± 0.3	38.0 ± 0.3	37.5 ± 0.3	37.8 ± 0.2

Values are mean ± SD. Prevasopressor measurements were performed immediately before the initiation of the vasopressor drug infusion.

AVP = arginine vasopressin; NE = norepinephrine; PE = phenylephrine; total IV anesthesia (TIVA) = fentanyl and midazolam infusion; ISO = fentanyl and isoflurane; MAP = mean arterial blood pressure; ICP = intracranial pressure; CPP = cerebral perfusion pressure; PbtO₂ = brain tissue oxygen tension; CBF = cerebral blood flow.

* $P < 0.05$ when comparing TIVA prevasopressor data with ISO prevasopressor data.

† $P < 0.05$ when comparing maximal dose response of vasopressor to prevasopressor data within group.

†† $P < 0.05$ when comparing maximal dose response of vasopressor between TIVA and ISO.

There were no differences noted between anesthetic groups in the average maximal doses of each vasopressor (Table 2).

Mean Arterial Blood Pressure

Initial MAP values, before initiation of the vasopressor (pre-vasopressor), were similar within each anesthetic group but initial MAP was lower in the ISO group compared with the TIVA group for all vasopressors (Table 3). Comparison of MAP values at the maximal dose of each vasopressor was similar between ISO and TIVA groups (Table 3). Additionally, all 3 vasopressors were able to achieve a statistically significant increase in MAP between baseline and maximal dose of vasopressor values, regardless of anesthesia used (Table 3). Two-way ANOVA analysis investigating the effects of vasopressor dose and anesthetic group on MAP for each vasopressor revealed significant vasopressor dose effects for all vasopressors ($P < 0.05$), but anesthetic choice had no significant effect on MAP.

Intracranial Pressure

During exposure to AVP, no change in ICP was observed regardless of dose or anesthetic exposure (Table 3). In contrast, NE exposure in the ISO group produced increases in ICP that were not observed in the TIVA group. During PE administration, piglets in both anesthetic groups displayed similar statistically significant increases in ICP compared with baseline.

Cerebral Perfusion Pressure

At the maximal dose of each vasopressor, CPP increased significantly above baseline for all groups (Table 3), except NE in the TIVA group ($P = 0.068$).

Brain Tissue Oxygen Tension

During the AVP portion of the experiment, piglets in both groups displayed no difference between $PbtO_2$ at the maximal dose of the vasopressor when compared with the pre-AVP values within groups. Additionally, pre-AVP and maximal dose AVP $PbtO_2$ values themselves were similar between groups (Table 3). In both TIVA and ISO groups, there was an increase in $PbtO_2$ when exposed to NE (2-way ANOVA analysis, $P < 0.05$). TIVA and ISO piglets had similar pre-NE values, but $PbtO_2$ was higher at maximal NE dose for ISO than for TIVA (Table 3) ($P < 0.05$). Pre-PE $PbtO_2$ values were higher in the ISO group, as were $PbtO_2$ values at the maximal dose of PE ($P < 0.05$). On 2-way ANOVA analysis of PE, both TIVA and ISO groups demonstrated a significant vasopressor dose effect on $PbtO_2$ ($P < 0.05$).

CBF and CVR

Normalized CBF (CBF at each dose divided by the pre-vasopressor CBF for each piglet) was evaluated via a 2-way ANOVA for each of the 3 vasopressors (Fig. 1) to evaluate the effects of vasopressor dose and anesthetic. Normalized CBF increased with escalating doses of NE and PE, but not AVP ($P = 0.02$, $P = 0.03$, $P = 0.93$, respectively) regardless of anesthetic group. Additionally, increases in normalized CBF were greater for the ISO group than TIVA group when exposed to NE or PE, but not AVP ($P = 0.03$, $P = 0.01$, $P = 0.14$, respectively). A group \times dose effect was only statistically significant for PE (PE, $P = 0.005$; NE, $P = 0.06$; AVP, $P = 0.55$).

At each dose of each vasopressor, a CVR, defined as CPP/CBF, and normalized CVR (CVR at a given vasopressor dose divided by the baseline CVR before vasopressor initiation) were calculated.³⁶ The normalized CVR was >1 for all doses with AVP and PE with TIVA, indicating cerebrovascular vasoconstriction with a vasopressor-induced increase in MAP (Fig. 2, A and C). By contrast, the CVR was consistently <1 for NE and PE with ISO (Fig. 2, B and C), indicating a vasodilatory pattern with vasopressor-augmented MAP. Normalized CVR while piglets were exposed to NE with TIVA was not exclusively >1 , but was consistently higher than piglets exposed to NE with ISO (Fig. 2B), supporting similar findings to the other vasopressors.

DISCUSSION

In summary, animals anesthetized with ISO had significantly larger increases in CBF compared with TIVA when exposed to escalating doses of NE or PE despite similar MAP and CPP responses. We were able to calculate CVR and observe decreases in CVR with escalating doses of PE and NE solely in the ISO group. This provides some initial experimental evidence that the vasopressor effect on cerebrovascular hemodynamics and autoregulation is influenced by anesthetic choice.

We investigated changes in CBF within a range of MAP and CPP with 3 different vasopressors. All 3 vasopressors were effective at increasing MAP in both anesthetic groups, indicating that all 3 are acceptable choices as drugs of therapeutic hypertension. However, we noted interesting differences in ICP between the TIVA and ISO groups. Specifically, AVP did not show any changes in ICP in either anesthetic group. PE had a statistically significant increase in ICP in the TIVA group, which was even more pronounced in the ISO

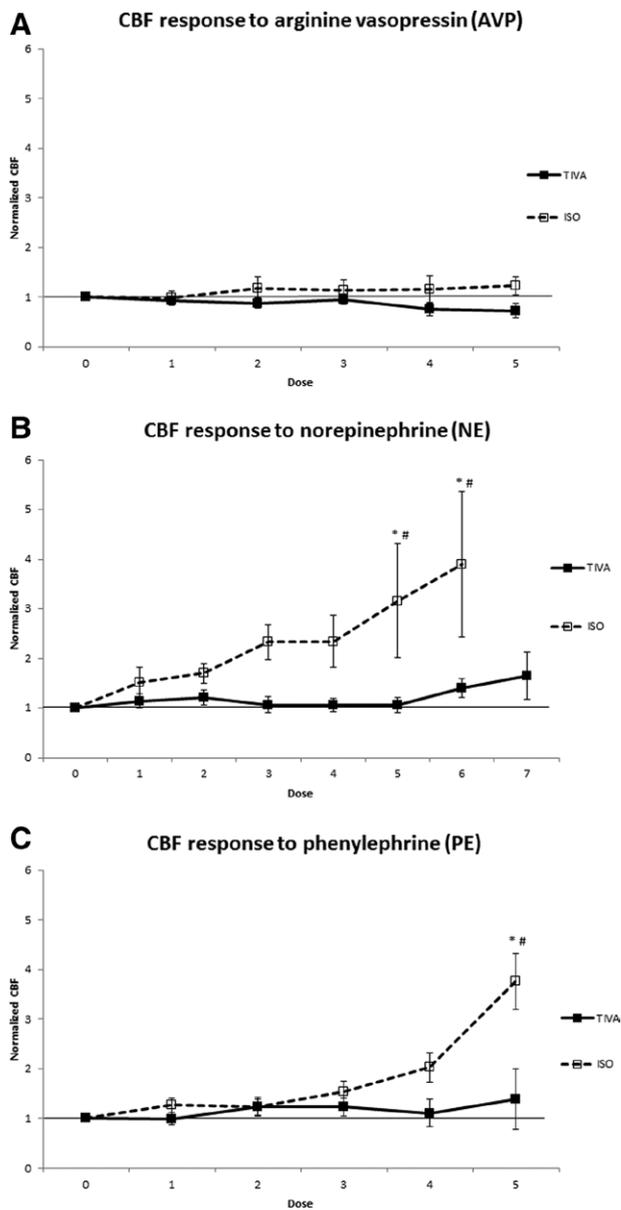


Figure 1. A, Normalized cerebral blood flow (CBF) response to arginine vasopressin (AVP) with fentanyl/midazolam total IV anesthesia (TIVA) (solid line and filled squares) versus fentanyl/isoflurane (ISO) (dotted line and open squares). B, Normalized CBF response to norepinephrine (NE) using TIVA (solid line and filled squares) versus ISO (dotted line and open squares). C, Normalized CBF response to phenylephrine (PE) with TIVA (solid line and filled squares) versus ISO (dotted line and open squares). * $P < 0.05$. $n = 8$ for all data points unless otherwise noted (# $n = 6$).

group. NE also demonstrated an increase in ICP only within the ISO group. With further increases in CBF due to exposure to NE and PE, the ISO group demonstrated statistically significant increases of ICP and alterations in CBF compared with TIVA. We speculate that the β activity of NE and the potential for smaller increases of central venous pressure³⁷ are possible explanations for the differences in ICP within the TIVA group, when comparing it with PE. Alternatively, the increased ICP observed with catecholamines may be attributable to effects on the blood-brain permeability by catecholamines and ISO.^{38,39} The maximal ICP increases observed

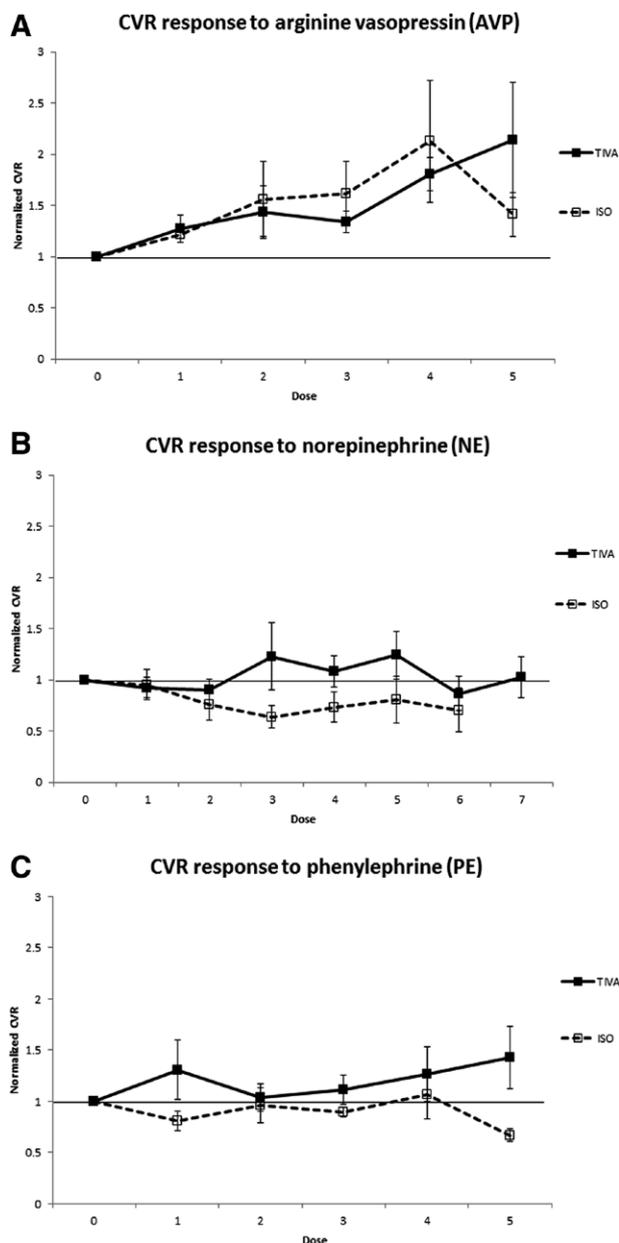


Figure 2. A, Normalized cerebrovascular resistance (CVR) response to arginine vasopressin (AVP) under fentanyl/midazolam total IV anesthesia (TIVA) (solid line and filled squares) versus fentanyl/isoflurane (ISO) (dotted line and open squares). B, Normalized CVR response to norepinephrine (NE) with TIVA (solid line and filled squares) versus ISO (dotted line and open squares). C, Normalized CVR response to phenylephrine (PE) with TIVA (solid line and filled squares) versus ISO (dotted line and open squares).

were below clinical thresholds for intracranial hypertension (in an uninjured brain), but it is unclear whether the magnitude of the ICP increases would be larger in the presence of intracranial pathology, and future studies in a model of intracranial hypertension are warranted.

CBF was measured continuously using thermal diffusion methodology. The TIVA group showed no difference between baseline CBF and CBF at maximal dose for any of the 3 vasopressors. This is the normal physiologic response to increased MAP or CPP and argues for an intact pressure

autoregulation within the TIVA group. For AVP and PE, normalized CVR was >1 for all doses of vasopressors within TIVA, indicating vasoconstriction with increasing doses. NE-normalized CVR values were consistently higher within the TIVA group than in the ISO group, but not exclusively >1 . Similar to the TIVA group, AVP exposure in the ISO group did not show a statistically significant change in CBF, with normalized CVR >1 , supporting the presence of intact pressure autoregulation. In contrast, arterial blood pressure modulation with NE and PE in the ISO group increased CBF indicating loss of pressure autoregulation. This was further supported by normalized CVR values consistently <1 indicating inappropriate decreases in CVR with increasing MAP and CPP. Alternative but less likely explanations for the observed increases in CBF in the ISO group include direct vasodilation of the cerebral vasculature by ISO or possibly NE, or increases in $CMRO_2$ metabolic rate with increases in vasopressor dosing resulting in matched increases in CBF.

The implication of this lack of pressure autoregulation has clinical importance. There are several clinical scenarios in which vasopressors would be used in the PICU without intracranial pathology such as sepsis, trauma without head injury, and acute respiratory distress syndrome. Some of these pediatric critically ill patients may require operative intervention and during that intervention may be transitioned to volatile anesthetics from their IV infusions. This may lead to significant changes in CBF and cerebrovascular responses to vasopressor infusions and may be a consideration in anesthetic choice when such dysautoregulation with increased ICP could be deleterious.

There are several limitations to our experimental design that must be considered when translating our results to pediatric patients. First, intramuscular ketamine, which is not frequently used in the pediatric neurocritical care practice, was administered in both anesthetic groups to facilitate induction. Ketamine exposure was an average of 120 minutes before baseline data acquisition, at which time there was no evidence of increased ICP to raise concern for adverse effects of ketamine. Second, ISO was used in both groups, including TIVA, for induction and instrumentation. ISO exposure was limited in duration, flushed from the ventilator system to minimize continued exposure, and average latency between discontinuation of ISO and baseline data acquisition was more than 30 minutes. Planes of anesthesia may not be exactly analogous between the TIVA and ISO groups, which may limit the ability to draw a conclusion on the relative impact on baseline CBF between anesthetics. However, both groups displayed a present reflexive withdrawal of the hind leg to painful stimuli, heart rate was similar between the groups, and no neuromuscular blockade was used throughout the studies suggesting similar anesthetic depths. Clinically, this seems to be of limited concern, because dosing was targeted to anesthetic effect. Of note, this study does not absolve midazolam and fentanyl infusions from deleterious cerebral circulation effects. Rather, our intent was to model the current standard of care in the PICU and compare it with a common anesthetic used for PICU patients undergoing operative procedures. $PbtO_2$ values were lower in the TIVA group, which may be related to decreases in $CMRO_2$, but its clinical consequence

is unclear. Vasopressor pharmacodynamic data are limited in immature swine and we cannot exclude any residual effects from our studies. However, the washout period was not terminated until physiologic variables had returned to baseline. Baseline CPP was lower in the ISO group, which raises the concern of whether or not CPP was below the lower limit of autoregulation. Previous studies of immature swine have reported the lower limits of autoregulation at a much lower CPP than the ISO group.⁴⁰ Finally, AVP was used as the target of the V1 receptor, despite the endogenous vasopressin molecule for piglets being lysine vasopressin.²⁹ AVP has been used in piglet models and is still an effective agent for achieving arterial hypertension.^{26,29,41,42}

Within this immature large-animal model, cerebral pressure autoregulation when challenged by vasopressor support (with PE or NE) was preserved using fentanyl and midazolam infusions, whereas it was adversely affected with ISO. Differences in cerebrovascular hemodynamic responses using IV versus volatile anesthetics have implications on choice of anesthetic and vasopressor for the care of the critically ill child requiring operative management, especially in those for whom impairment of cerebral autoregulation may be expected to have deleterious effects. Furthermore, selection of anesthetic drugs for large-animal models is critical to investigate mechanisms of cerebrovascular hemodynamics, and in translating critical care investigations between the laboratory and bedside. ■■

DISCLOSURES

Name: Benjamin Bruins, MD.

Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.

Attestation: Benjamin Bruins has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

Name: Todd J. Kilbaugh, MD.

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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.

Attestation: Susan S. Margulies has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

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Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.

Attestation: Stuart H. Friess has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

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