Dose-Dependent Hemodynamic and Metabolic Effects of Vasoactive Medications in Normotensive, Anesthetized Neonatal Piglets

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ABSTRACT: The developmentally regulated hemodynamic effects of vasoactive medications have not been well characterized. We used traditional and near-infrared spectroscopy monitoring technologies and investigated the changes in heart rate, blood pressure, common carotid artery (CCA) blood flow (BF), cerebral, renal, intestinal, and muscle regional tissue O_2 saturation, and acid-base and electrolyte status in response to escalating doses of vasoactive medications in normotensive anesthetized neonatal piglets. We used regional tissue O_2 saturation and CCA BF as surrogates of organ and systemic BF, respectively, and controlled minute ventilation and oxygenation. Low to medium doses of dopamine, epinephrine, dobutamine, and norepinephrine increased blood pressure and systemic and regional BF in a drug-specific manner, whereas milrinone exerted minimal effects. At higher doses, dopamine, epinephrine, and norepinephrine but not dobutamine decreased systemic, renal, intestinal, and muscle BF, while cerebral BF remained unchanged. Epinephrine induced significant increases in muscle BF and serum glucose and lactate concentrations. The findings reveal novel drug- and dose-specific differences in the hemodynamic response to escalating doses of vasoactive medications in the neonatal cardiovascular system and provide information for future clinical studies investigating the use of vasoactive medications for the treatment of neonatal cardiovascular compromise. (*Pediatr Res* 70: 473–479, 2011)

Cardiovascular compromise is a frequently encountered condition in the critically ill preterm and term infant (1) resulting in inadequate tissue O_2 delivery, impaired cerebral blood flow (CBF) autoregulation, and, potentially, end-organ injury and death (1–3). Our limited ability to accurately monitor changes in neonatal hemodynamics curtails timely recognition, and thus treatment, of neonatal shock.

Although vasopressor-inotropes, inotropes, and lusitropes have been used to manage neonatal cardiovascular compro-mise with an attempt to tailor the treatment to the suspected primary etiology (1), there is only limited information available on the safety and effectiveness of these medications (1,4) and little is known about their developmentally regulated dose-dependent hemodynamic actions (4,5). Recent advances in bedside hemodynamic monitoring techniques using, among others, near-infrared spectroscopy (NIRS) have made continuous, noninvasive monitoring of tissue O_2 delivery (6) possible. Accordingly, data on tissue O_2 delivery and utilization (7) and regional O_2 saturation in critically ill adults, children, and, more recently, neonates have become available (2,3,8–10).

To gain insight into the specific, drug-related changes in neonatal hemodynamics, we used traditional and NIRS hemodynamic monitoring technologies and investigated the changes in heart rate, blood pressure (BP), common carotid artery (CCA) blood flow (BF), cerebral regional tissue O_2 saturation ($CrSO_2$), renal (kidney) regional tissue O_2 saturation ($KrSO_2$), intestinal (gut) regional tissue O_2 saturation ($GrSO_2$), muscle regional tissue O_2 saturation ($MrSO_2$), and acid-base and electrolyte status in response to escalating doses of vasopressor-inotropes, inotropes, and lusitropes in normotensive anesthetized neonatal piglets.

MATERIALS AND METHODS

Surgical preparation and laboratory measurements. Neonatal Yorkshire Duroc piglets of 10 ± 3 d of age weighing 2.4 ± 0.6 kg were preanesthetized with ketamine (33 mg/kg) and atropine (0.05 mg/kg), intubated, and anesthetized using 1.5–3.0% isoflurane while mechanically ventilated (Draeger Medical Apollo Anesthesia Machine; Draeger, Germany). Core body temperature was maintained at 38 ± 0.5°C and BP, heart rate, arterial O_2 saturation (SpO_2; Datex-Ohmeda, GE Healthcare, Milwaukee, WI), end-tidal CO_2, fraction of inspired O_2, and pulmonary compliance (Medical Apollo Anesthesia Machine; Draeger, Germany) were continuously monitored. Heart rates beyond 250 bpm were captured by the PC-Vet wireless ECG system (Vmed Technology, Mill Creek, WA) or, rarely, by direct counting. Following skin preparation, NIRS sensors were placed on the head, the dorsal abdomen over

Abbreviations: BF, blood flow; **BP,** blood pressure; **CBF,** cerebral blood flow; **CCA,** common carotid artery; **CrSO₂, KrSO₂, GrSO₂, MrSO₂,** regional tissue O_2 saturation of brain, kidney, gut, and muscle, respectively; **NIRS,** near-infrared spectroscopy; **PaO₂,** partial arterial O_2 pressure; **Paco₂,** partial arterial CO_2 pressure; **rSO₂,** regional tissue O_2 saturation; **SpO₂,** arterial O_2 saturation
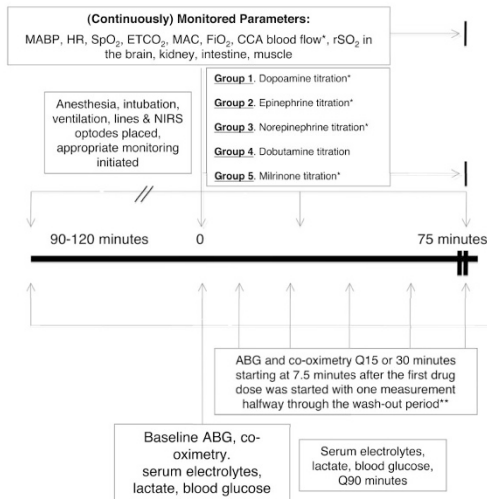
Figure 1. Experimental protocol. *, CCA BF was not monitored in all animals; **, ABGs were obtained every 15 or 30 min to ensure that pH, $Paco_2$, and base excess were within the target ranges. ABG, arterial blood gas; HR, heart rate; $ETCO_2$, end-tidal CO_2; FiO_2, fraction of inspired oxygen; MABP, mean arterial BP; MAC, mean alveolar concentration (of anesthetics). See text for details.

the right kidney, the abdomen lateral to the umbilicus, and the right leg over the gluteus muscle, and regional tissue O_2 saturation (rSO_2) of the brain, kidney, gut, and muscle was monitored continuously by an INVOS regional tissue oxygenation monitor (INVOS 5100C, Somanetics, Troy, MI).

Serum electrolytes, glucose, lactate and Hb concentration, and arterial blood gasses were followed by iSTAT (Abbott Point of Care, Inc., Princeton, NJ) as per the experimental protocol (Fig. 1). Animals received i.v. heparin (200 units/kg/h), physiologic saline (10 mL/kg/h), and 10 g/dL of dextrose-water to adjust serum glucose levels using Genie Plus syringe pumps validated for stability of infusion rate (Kent Scientific, Torrington, CT). Serum electrolytes, pH (7.20–7.45), base excess (-6 to $+6$), partial arterial O_2 pressure (Pao_2; 80–120 mm Hg) and partial arterial CO_2 pressure ($Paco_2$; 35–45 mm Hg), and SpO_2 (90–100%) were maintained in the target ranges using sodium bicarbonate, potassium chloride, lactated Ringer's solution, and ventilatory changes, respectively.

Both femoral veins and left femoral artery were cannulated for fluid and drug administration and arterial BP measurements and blood sampling, respectively. In three of the seven animals in the studies with dopamine, epinephrine, dobutamine, and milrinone, and in all four animals in the norepinephrine experiments, the CCA was instrumented for continuous BF measurements using an ultrasonic flow-meter (T400; Transonic Systems, Inc., Ithaca, NY). Urine output was not measured because of technical difficulties associated with catheterization of newborn piglets. Data were collected real time at sampling rates between 9 and 240 samples/min and stored on a computer for offline analysis (The RugLoop Program, D_{med}, Temse, Belgium).

Experimental protocols. The study was approved by the Institutional Animal Care and Use Committee at Providence Hospital, Detroit, MI.

Stability studies. Four piglets without CCA flow measurements were monitored for 4 h to document cardiovascular stability of the preparation.

Dose-escalation studies. Changes in the hemodynamic parameters and serum electrolyte, lactate, and glucose and Hb concentration were followed during graded doses of selected vasoactive medications. After a 15-min postsurgical stabilization period, baseline measurements were recorded, followed by dose escalation and a 15-min washout period after discontinuation of the medication (Fig. 1). Except for milrinone, each drug dose was given for 15 min.

Group 1 (seven animals): dopamine was administered in concentrations of 5, 10, 15, 20, 25, and 30 $\mu g/kg/min$.
Group 2 (seven animals): epinephrine was administered in concentrations of 0.25, 0.5, 0.75, 1.0, 1.5, and 2.0 $\mu g/kg/min$.
Group 3 (four animals): norepinephrine was administered in concentrations of 0.25, 0.5, 0.75, 1.0, 1.25, and 1.5 $\mu g/kg/min$.
Group 4 (seven animals): dobutamine was administered in concentrations of 5, 10, 15, 20, 25, and 30 $\mu g/kg/min$.

Group 5 (six animals): milrinone was administered as a bolus of 50 $\mu g/kg$ over 15 min followed by continuous infusions of 0.375 $\mu g/kg/min$ and 0.75 $\mu g/kg/min$, each given for 30 min.

Statistical analysis
Hemodynamic parameters. A computer code in MatLab (MathWorks, Natick, MA) was written for loading, processing, and statistical analysis of the data from the RugLoop program.

The mean values of the hemodynamic parameters were first calculated for every 1-min block followed by calculation of the mean values of the last 5 min of each dose block. We assumed that the last 5 min of each dose block represented the equilibrium of the effects at each dose most accurately. ANOVA was used to determine statistical significance among the mean values of the last 5-min blocks. If these findings were statistically significant, a pairwise comparison using Tukey-multiple comparison was performed.

To determine the rate of change of the hemodynamic parameters, the data obtained were subdivided into "baseline," "low dose" (first drug dose), "medium dose" (second and third drug doses), "high dose" (fourth-sixth drug doses), and "postmedication" blocks. The slopes of changes in each block were calculated from the best linear fit to the data (MatLab-Regression Diagnostics, Natick, MA), and the R^2 value for the goodness of fit was determined. The slopes between BP and $CrSO_2$, BP and CCA BF, and CCA BF and $CrSO_2$ were tested for statistical difference using F-statistics (MatLab-Linear Hypothesis Test; Natick, MA). The $p < 0.05$ was considered significant.

Laboratory measurements. Data are given as mean $\pm$ SD unless indicated otherwise. ANOVA for repeated measures (ANOVA-RM. SPSS, Chicago, IL, release 18.0.0) was used where more than two datasets were available for the given parameter. In case of statistical significance, a pairwise comparison with Bonferroni adjustment was performed. For laboratory tests with two measurements across the dose-escalation experiments, paired t test was used. The $p < 0.05$ was considered significant.

RESULTS

Stability studies. In the four animals studied to assess the stability of the preparation over time, all hemodynamic parameters monitored (data not shown) and, except for the initial serum glucose concentration, all laboratory parameters remained stable and within the target range for 4 h (Table 1; serum electrolytes and Hb values not shown). Based on these findings, the initial glucose delivery rate was adjusted in the dose-escalation experiments.

Dose-escalation studies
Group 1. Dopamine (5–30 $\mu g/kg/min$) caused dose-dependent increases in heart rate, BP, $CrSO_2$, $KrSO_2$, $GrSO_2$, and CCA flow (Fig. 2A). However, the pattern of changes was different among the hemodynamic parameters. The increase in BP and $CrSO_2$ paralleled at the low- and medium-dose blocks ($p = 0.7$ and 0.19, respectively). In the high-dose block (20–30 $\mu g/kg/min$), the slopes of BP and $CrSO_2$ differed as BP tended to increase while $CrSO_2$ remained unchanged ($p < 0.001$). At medium doses, CCA BF increased out of proportion of the increase in BP ($p < 0.001$) and slightly decreased in the high-dose block, whereas BP continued to rise ($p < 0.001$). At the lowest dose, $KrSO_2$ and $GrSO_2$ increased significantly and out of proportion of the change in BP. Among all drugs tested, dopamine increased $GrSO_2$ the most (Fig. 3C). Higher doses of dopamine tended to attenuate the increases in $KrSO_2$ more than in $GrSO_2$. No apparent changes in $MrSO_2$ were noted. On discontinuation of dopamine, all values returned toward or below baseline. The same pattern was seen in the washout phase with the other medications. Among the laboratory parameters, only serum glucose (Table 1) and Hb increased.

Group 2. Epinephrine (0.25–2 $\mu g/kg/min$) increased heart rate in a dose-dependent manner. At lower doses, BP, CCA

Table 1. *Average blood gas and serum lactate and glucose values during the stability ("control") experiments and the dose-escalation studies*

	Time	0 min	30 min	60 min	90 min
Control	pH	7.39 ± 0.03	7.38 ± 0.04	7.39 ± 0.06	7.39 ± 0.06
	pCO_2	36.2 ± 5.0	36.9 ± 3.7	34.2 ± 2.4	34.9 ± 1.2
	BE	-3.0 ± 3.65	-3.0 ± 3.86	-4.0 ± 3.83	-3.5 ± 3.87
	Lactate	1.77 ± 0.96	1.78 ± 0.97	1.78 ± 0.95	1.7 ± 1.04
	pO_2	113.0 ± 12.8	106.8 ± 11.9	113.2 ± 6.8	113.8 ± 13.1
	Glucose	217.2 ± 198.6		124.0 ± 43.6	
Dopamine	pH	7.36 ± 0.04	7.35 ± 0.04	7.33 ± 0.06	7.33 ± 0.07
	pCO_2	39.1 ± 4.2	39.8 ± 3.7	40.9 ± 4.1	40.7 ± 5.9
	BE	-3.6 ± 2.94	-3.6 ± 2.99	-4.3 ± 2.98	-4.3 ± 2.98
	Lactate	2.1 ± 0.92	2.1 ± 0.87	2.0 ± 0.67	2.1 ± 0.64
	pO_2	103.7 ± 4.7	101.7 ± 9.7	98 ± 15.2	92.7 ± 12.8
	Glucose	$109.3 \pm 36.5*$			$145.9 \pm 53.7†$
Epinephrine	pH	$7.39 \pm 0.08*$	7.31 ± 0.06	$7.26 \pm 0.07†$	$7.26 \pm 0.04†$
	pCO_2	37.1 ± 5.56	41.9 ± 4.55	43.0 ± 8.72	40.8 ± 6.76
	BE	$-3.57 \pm 3.26*$	-5.8 ± 2.78	$-8.0 \pm 3.65†$	$-8.86 \pm 3.29†$
	Lactate	$2.13 \pm 0.51*$	3.43 ± 1.08	$5.28 \pm 1.02†$	$6.76 \pm 1.16†$
	pO_2	$126.4 \pm 17.7*$	$98 \pm 17.8†$	98 ± 15.6	$98.6 \pm 10.4†$
	Glucose	$168.0 \pm 41.8*$			$357.7 \pm 45.2†$
Norepinephrine	pH	7.33 ± 0.03	7.31 ± 0.07	7.32 ± 0.10	7.3 ± 0.7
	pCO_2	41.9 ± 0.5	43.3 ± 6.2	43.9 ± 9.2	40.3 ± 6.3
	BE	-3.8 ± 1.5	-4.5 ± 1.9	-4.3 ± 2.6	-4.8 ± 2.9
	Lactate	1.7 ± 0.6	1.8 ± 0.9	2.2 ± 0.6	2.9 ± 0.6
	pO_2	97.8 ± 11.3	95.0 ± 10.2	90.3 ± 5.1	90.5 ± 6.1
	Glucose	$122.8 \pm 29.9*$			$209.8 \pm 21.8†$
Dobutamine	pH	7.3 ± 0.04	7.3 ± 0.04	7.3 ± 0.03	7.3 ± 0.05
	pCO_2	41.0 ± 4.7	43.4 ± 6.3	40.7 ± 4.2	40.5 ± 3.9
	BE	-3.75 ± 1.62	-4.14 ± 2.48	-4.14 ± 2.04	-4.71 ± 2.50
	Lactate	1.73 ± 0.78	1.61 ± 0.82	1.68 ± 0.85	1.85 ± 0.90
	pO_2	111.4 ± 9.8	94.6 ± 12.9	97.6 ± 16.6	92.7 ± 17.9
	Glucose	$109.4 \pm 38.8*$			$134.9 \pm 26.9†$
Milrinone	pH	7.38 ± 0.05	7.43 ± 0.18	7.37 ± 0.05	
	pCO_2	33.1 ± 5.9	35.52 ± 5.4	35.4 ± 5.4	
	BE	-5.67 ± 3.72	-5.17 ± 3.19	-5.00 ± 3.35	
	Lactate	3.08 ± 1.83	2.66 ± 0.89	2.71 ± 0.58	
	pO_2	116.5 ± 11.5	109.7 ± 9.7	106.0 ± 11.8	
	Glucose	175.3 ± 90.2		142.3 ± 43.2	

Data marked with asterisk (*) are statistically significantly different from data marked with the symbol "†." For the experiments of milrinone, complete datasets were also available for "15 and 45 min" (not shown), and these data were included in the statistical analysis. See text for details.

"0 minutes," before initiation of drug infusion; "90 minutes" (60 minutes for the experiments with milrinone), during the highest dose of the given medication; BE, base excess; n, sample size.

flow, $CrSO_2$, $KrSO_2$, $GrSO_2$, and $MrSO_2$ increased significantly (Fig. 2*B*), and the increase in $KrSO_2$ was similar to that seen with low to medium doses of dopamine (Fig. 3*B*). As with dopamine, the increase in BP and $CrSO_2$ paralleled in the low- and medium-dose blocks ($p = 0.108$ and 0.995, respectively). At higher doses of epinephrine, CCA flow, $KrSO_2$, $GrSO_2$, and $MrSO_2$ gradually decreased; $CrSO_2$ remained unchanged; and BP continued to rise (BP *versus* $CrSO_2$ slope; $p < 0.001$). Among the medications tested, low, medium, and high doses of epinephrine caused the most significant increase in $MrSO_2$, CCA flow, and BP, respectively (Fig. 3*D*). BP and CCA flow showed a low-frequency high-amplitude oscillatory pattern. $KrSO_2$, $GrSO_2$, and $MrSO_2$ followed the oscillations but $CrSO_2$ did not. Serum glucose and lactate and Hb increased, and pH and base excess decreased (Table 1). Epinephrine caused the most significant increase in serum glucose and lactate (Table 1).

Group 3. At $0.25 \, \mu g/kg/min$, norepinephrine did not affect the hemodynamic parameters (Fig. 2*C*). At $0.5 \, \mu g/kg/min$ the drug abruptly increased heart rate, BP, CCA BF, $CrSO_2$, and

$MrSO_2$ and to a lesser extent $GrSO_2$ and $KrSO_2$. Among the medications studied, norepinephrine caused the most abrupt and single-dose-related increase in BP, CCA BF, and $CrSO_2$ (Fig. 2*C*). In the medium- and high-dose blocks, the slopes of $CrSO_2$ and BP did not differ ($p = 0.36$ and 0.31, respectively). At higher doses, CCA flow, $KrSO_2$, $GrSO_2$, and $MrSO_2$ were significantly attenuated. In the high-dose block, the BP tracing revealed a low-frequency oscillatory pattern with variable amplitude and without changes in the baseline (slope $= 0.06 \pm 0.01$). As with epinephrine, CCA flow, $GrSO_2$, and $KrSO_2$, but not $CrSO_2$, mirrored the oscillations on BP. Serum chloride and glucose and Hb increased, while serum lactate trended to increase (Table 1).

Group 4. Dobutamine ($5–30 \, \mu g/kg/min$) increased heart rate in a dose-dependent manner (Fig. 2*D*). At doses of 5 and 10 $\mu g/kg/min$, $CrSO_2$, $KrSO_2$, $GrSO_2$, and BP increased in a dose-dependent manner. The slopes of BP and $CrSO_2$ and BP and CCA flow were different in the medium- and high-dose blocks ($p < 0.001$ for both comparisons). BP and CCA flow increased abruptly at 10 $\mu g/kg/min$ followed by small in-
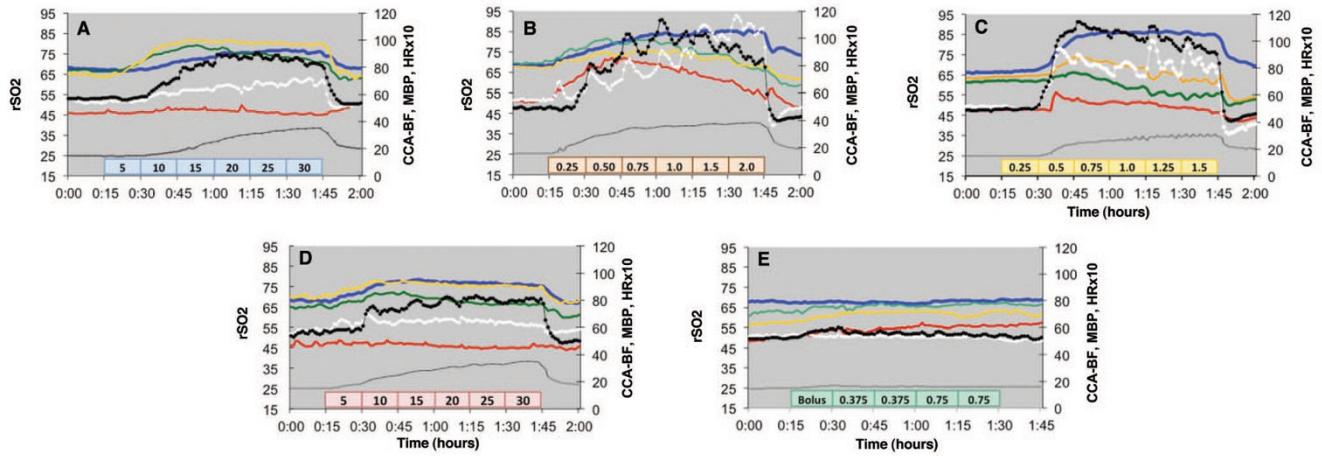
Figure 2. Hemodynamic effects of escalating doses of dopamine (*A*), epinephrine (*B*), norepinephrine (*C*), dobutamine (*D*), and milrinone (*E*). Changes in heart rate (HR; 1/min; shown as actual rate divided by 10), mean BP (MBP; mm Hg), and CCA BF (mL/min) on the right y axis and CrSO$_2$ (%), KrSO$_2$ (%), GrSO$_2$ (%), and MrSO$_2$ (%) on the left y axis are shown before, during, and after the experiments with dopamine (*A*; $n = 7$; CCA-flow = 3), epinephrine (*B*; $n = 7$; CCA-flow = 3), norepinephrine (*C*; $n = 4$; CCA-flow = 4), dobutamine (*D*; $n = 7$; CCA-flow = 3), and milrinone (*E*). Except for milrinone, each dose was given for 15 min, and the escalating doses (mcg/kg/min) are shown in each panel above the x axis in colored boxes. See text for details. CCA-BF (*black*); CrSO$_2$ (*blue*); GrSO$_2$ (*gold*); heart rate (HR) × 10 (*gray*); KrSO$_2$, (*green*); mean BP (MBP) (*white*); MrSO$_2$ (*red*).
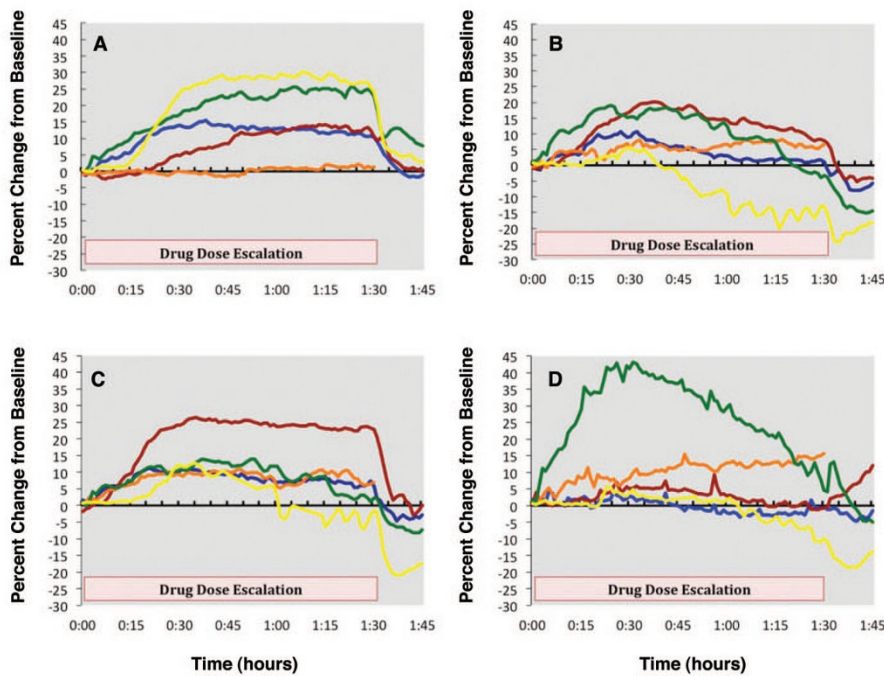

Figure 3. Relative organ-specific changes in rSO$_2$ in response to infusion of escalating doses of vasoactive medications. Relative changes compared with baseline in CrSO$_2$ (*A*), KrSO$_2$ (*B*), GrSO$_2$ (*C*), and MrSO$_2$ (*D*) (y axis) in response to advancing doses of dopamine (*brown*), epinephrine (*green*), norepinephrine (*yellow*), dobutamine (*blue*), and milrinone (*gold*) are shown (time in hours on the x axis). The relative protection of CBF from vasoconstriction is suggested by the lack of a decrease in CrSO$_2$ at high doses of vasopressor-inotropes (*A*). See text for details.

creases in CCA flow but not in BP. Although the magnitude of the BP increase was similar to that seen with dopamine, the dobutamine-induced increases in CCA flow, GrSO$_2$, and KrSO$_2$ were smaller (Figs. 3*A*-*C*). No significant changes in MrSO$_2$ occurred while serum glucose and Hb slightly increased (Table 1).

Group 5. The 50 μg/kg bolus of milrinone caused a slight increase in heart rate, CCA BF, KrSO$_2$ GrSO$_2$, and MrSO$_2$ (Fig. 2*E*). During the dose-escalation phase, BP, heart rate, and CCA flow decreased toward or slightly below baseline, CrSO$_2$, KrSO$_2$, and MrSO$_2$ remained unchanged and MrSO$_2$ continued to slightly increase (Fig. 2*E*). As BP tended to decrease during the dose-escalation phase, a significant difference between the slopes of BP and CrSO$_2$ was noted in the high-dose block ($p < 0.001$). All laboratory parameters remained stable (Table 1).

DISCUSSION

To our knowledge, this is the first study investigating the developmentally regulated dose-dependent effects of dopamine, epinephrine, norepinephrine, dobutamine and milrinone on heart rate, BP, systemic and organ BF, O$_2$ delivery, and

acid-base and electrolyte status. Our findings reveal significant drug- and dose-specific differences in the hemodynamic and metabolic response among these vasoactive medications in normotensive anesthetized neonatal piglets.

We measured CCA BF directly and assessed BF changes to the brain, kidneys, intestine, and muscle by monitoring rSO_2, using NIRS. As long as metabolic rate and oxygenation remain unchanged, changes in rSO_2 reflect changes in regional BF (7,11). In our study, SpO_2 and Pao_2 remained unchanged and, with the exception of epinephrine (12), metabolic rate is unlikely to have changed during the experiments. Therefore, we used rSO_2 as a surrogate of regional BF. Finally, because we kept $Paco_2$ and Pao_2, the most potent acute regulators of CBF (13) constant, we could assess the direct effects of vasoactive medications on CBF.

Dopamine exerts its complex cardiovascular, renal, and endocrine effects by the dose-dependent stimulation of the dopaminergic (low doses), beta-adrenergic (medium doses), alpha-adrenergic (high doses), and serotoninergic receptors (4). In our normotensive anesthetized neonatal piglet model, the drug caused the expected dose-dependent changes in heart rate, BP, and renal and mesenteric BF (4,14,15). Although selective dopaminergic renal and mesenteric vasodilation has been consistently documented in animals and humans across the spectrum of development (4,14,15), dopamine, between 2 and 32 μg/kg/min, did not affect renal and mesenteric BF in chronically instrumented, awake piglets (16). The reason for this finding is unclear but chronic instrumentation of the renal and superior mesenteric artery might have affected vasoreactivity in these vessels.

Because the changes in $CrSO_2$ and BP paralleled during low and medium doses of dopamine, CBF autoregulation was impaired in the anesthetized piglets. This finding is explained by the anesthesia-induced impairment of this protective vascular mechanism (17). The increase in CCA BF out of proportion of the increase in BP and $CrSO_2$ at low to medium doses suggests an increase in cardiac output and, perhaps, a selective dopaminergic vasodilation in the extracranial vessels of the neck and head (4). The findings that, at the highest doses, BP increased out of proportion to $CrSO_2$, whereas $KrSO_2$, $GrSO_2$, and CCA BF decreased suggest an alpha-adrenoreceptor-mediated peripheral vasoconstriction resulting in a decrease in cardiac output (4), a relative sparing of the cerebral vasculature from vasoconstriction and an impaired yet not completely diminished CBF autoregulation (4,13). The finding that the increase in $GrSO_2$ was greater at low to medium doses and was less attenuated at higher doses than that in $KrSO_2$ indicates that, similar to the immature rat (18) and unlike in the preterm neonate (15), dopamine induces a more pronounced mesenteric than renal vasodilation in the newborn piglet. These findings point to important interspecies differences in the hemodynamic response to dopamine. The small increase in $MrSO_2$ at low to medium doses of dopamine and the moderate increase in serum glucose suggest a limited peripheral β_2-adrenoreceptor stimulatory effect of the drug.

Dopamine had no effect on blood gasses and serum lactate and electrolytes. We speculate that the hemoconcentration observed by the end of the experiments was the consequence of increased urine output caused by both the hemodynamic and direct renal effects of dopamine (4,14). The observation that hemoconcentration only occurred with drugs causing both an increase in BP and adrenoreceptor stimulation (dopamine, epinephrine, norepinephrine, and dobutamine but not milrinone), supports this speculation.

Epinephrine exerts its complex cardiovascular, renal, and endocrine effects primarily by the dose-dependent stimulation of beta- and alpha-adrenergic receptors (19). As with dopamine, at low doses of epinephrine, there was evidence of impaired CBF autoregulation and an increase in renal and mesenteric BF and cardiac output (17). However, CBF autoregulation was not completely abolished because $CrSO_2$ did not mirror the fluctuations in BP, whereas CCA BF did. Based on the attenuated fluctuations in $KrSO_2$, $GrSO_2$, and $MrSO_2$, BF autoregulation functioned at the level expected for these organs. The fluctuations in BP might have been due to rapid desensitization of adrenergic receptors (1,20) and a myogenic and peripheral autonomic nervous system response to the abrupt increases in perfusion pressure. The significant increase in muscle BF at low and medium doses and the increase in serum glucose and lactate are due to the high affinity of epinephrine to β_2-adrenoreceptors (18) and underscore the physiological role of epinephrine in assisting the "fight-or-flight" response during stress (12). At the highest dose range, the alpha-adrenoreceptor-mediated vasoconstriction resulted in a decrease in BF to all organs but the brain, indicating a preservation of brain BF even at very high doses of epinephrine. Because BP continued to rise while CCA BF declined, cardiac output likely also decreased somewhat at high doses. These findings demonstrate a relative sparing of the cerebral vasculature from vasoconstriction and that epinephrine is a more potent vasopressor than dopamine (4,12,19).

The increase in serum glucose and lactate and the associated acidosis were because of the enhanced gluconeogenesis caused by the drug-induced β_2-adrenoreceptor stimulation (21). The lactic acidosis during low- to medium-dose epinephrine administration is not caused by excessive vasoconstriction (22) and has been described in neonatal piglets (23) and preterm neonates (24).

Norepinephrine exerts its complex cardiovascular and endocrine effects by the dose-dependent stimulation of beta- and alpha-adrenergic receptors (19). Compared with epinephrine, norepinephrine has more enhanced alpha- and minimal peripheral vascular beta adrenoreceptor stimulatory effects (19). Accordingly, the major differences in the hemodynamic response between norepinephrine and epinephrine are explained by the overwhelming peripheral vasoconstrictive actions of norepinephrine at medium-to high doses as BF to all organs but the brain decreased and CCA flow paralleled the decline in BP. Interestingly though, at a narrow dose range at low doses, norepinephrine increased BP and CCA and regional organ BFs. This finding maybe of clinical importance and suggests that low-dose norepinephrine increases cardiac output more than systemic vascular resistance even in the immature cardiovascular system. Because of its relatively decreased affinity to β_2-adrenoreceptors, norepinephrine increased serum glucose levels less than epinephrine (19). The cause of the small

but statistically significant increase in serum chloride concentration is unclear.

Dobutamine has relatively selective cardiac beta- and alpha-adrenoreceptor stimulatory effects (25). Accordingly, dobutamine administration results in direct inotropic and chronotropic actions and a variable decrease in systemic vascular resistance (19,25). Low and medium doses of dobutamine caused small increases in BP and relatively larger increases in CCA flow indicating an increase in cardiac output. Perhaps of clinical relevance is the finding that renal and mesenteric BF increased as much as by low-dose epinephrine. The modest increase in serum glucose and muscle BF suggests a weak affinity of dobutamine to β_2-adrenoreceptors.

Relatively selective phosphodiesterase type-III inhibitors such as milrinone exert their cardiovascular effects (positive inotropy, improved diastolic function, and vasodilation) primarily by increasing intracellular cAMP concentrations (26). Their positive inotropic effect has been documented in mature but not newborn (27) animals and children and adults (26,28). Milrinone exerted minimal hemodynamic and no metabolic effects in the normotensive piglets. The unchanged CBF in face of the slight decrease in BP suggests that cardiac output was maintained and CBF autoregulation was effective within the range of the BP changes. Interestingly, a recent study found that milrinone is as effective as epinephrine or dobutamine in improving cardiac output and systemic BP in asphyxiated neonatal piglets (29).

Although we controlled for the most important acute regulators of organ, especially brain BF, such as pH, Pa_{CO_2}, and Pa_{O_2}, our study has several limitations. First, we used rSO_2 as a surrogate of organ BF. We did this because oxygenation was maintained constant during the experiments and, except for epinephrine, which may have increased basic metabolic rate by 7–15% (12), metabolic rate is unlikely to have changed with the use of the other medications. Furthermore, because we documented a varying pattern of changes in rSO_2 among the different drugs, it is unlikely that these rapid organ-specific changes in rSO_2 were caused by changes in metabolic activity rather than in BF. Second, because cardiac output was not directly measured, changes in CCA BF were used as a surrogate to changes in cardiac output. As regional hemodynamic effects such as changes in CBF also affect CCA BF, in the discussion we always refer to changes in systemic BF in context of the changes in CBF. However, these interpretations must be viewed with caution. Third, direct measurement of CCA BF was not performed in all animals except for the experiments with norepinephrine. However, as the drug-specific hemodynamic response was similar among the animals in each group, it is unlikely that the CCA BF findings would have been affected by enrolling more animals with direct CCA BF measurements. Finally, because we used normotensive newborn piglets to investigate the hemodynamic effects of vasoactive medications, our findings may not fully apply to a neonatal animal model with cardiovascular compromise (29). To address this concern, we have recently completed a study investigating the effects of these vasoactive agents in neonatal piglets with endotoxin-induced shock (manuscript in preparation).

In summary, we have identified novel interactions between systemic BP and systemic and organ BF in response to escalating doses of vasoactive medications in normotensive anesthetized neonatal piglets. At low to medium doses, systemic BF and BP increased with dopamine, epinephrine, and dobutamine and, in a narrow dose range, with norepinephrine. We also found that the renal and mesenteric hemodynamic effects of dopamine, epinephrine, and dobutamine are similar although not identical. Among the metabolic effects, the epinephrine-induced hyperglycemia and, especially, lactic acidosis are of clinical relevance as the drug-induced lactic acidosis (22–24) prevents the use of serial serum lactate levels as an indirect marker of changes in BF during epinephrine administration. Finally, because of the interspecies differences, caution must be exercised when extrapolating the findings on systemic and regional hemodynamics to the human neonate. Accordingly, although the information obtained in this study is useful for the design of interventional clinical trials, future studies using complex hemodynamic monitoring approaches (30) in critically ill neonates need to confirm these findings before the information provided here can be applied to the clinical practice.

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