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Effects of Dopamine and Dobutamine on Regional Blood Flow Distribution in the Neonatal Piglet

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Objective

The authors determined the effects of dopamine and dobutamine on organ blood flow in newborn piglets.

Summary Background Data

Although the hemodynamic effects of dopamine and dobutamine are well described in adults, little is known of their consequences in neonates, and their impact on organ perfusion in premature infants is unclear.

Methods

Cannulae were placed in the femoral vessels and left atrium of term (1-14 days old) and prematurely delivered (Cesarean section at 90% of term gestation) piglets. After stabilization, radiolabeled microspheres were injected. A continuous infusion of dopamine or dobutamine was started, and other microspheres were injected at 5, 10, and 15-μg/kg/minute drug doses (allowing a 20-minute equilibration period at and between each dose). Blood flows (mL/minute/g tissue) to organs were determined using reference organ techniques.

Results

In term animals only, dobutamine and dopamine increased systemic mean arterial pressure at the 15-μg dose. In term piglets, dobutamine produced dose-dependent increases ($p < 0.05$, analysis of variance) in heart and brain blood flow, although small intestinal blood flow decreased (1.47 ± 0.13 mL/minute/g baseline to 1.31 ± 0.11 mL/minute/g at 15-μg dose). There were no significant changes in blood flow to these organs in preterm animals. Dopamine significantly ($p < 0.05$) increased heart blood flow in both groups. Dopamine also increased small intestinal blood flow in term (1.63 ± 0.22 mL/minute/g baseline to 3.13 ± 0.34 mL/minute/g at 15-μg dose) and premature (0.31 ± 0.10 mL/minute/g baseline to 1.11 ± 0.29 at 15-μg dose) piglets.

Conclusions

Dopamine may prove a valuable adjunct when a premature infant is at risk for conditions that reduce alimentary tract blood flow.

Dopamine and dobutamine frequently are used in the neonatal intensive care unit setting, particularly in circumstances where an infant has developed a decline in mean arterial pressure unresponsive to intravenous fluid challenges. The effects of each of these agents on both central hemodynamics and organ blood flows—particularly to the alimentary tract viscera—are well-delineated in adults and in term newborns.

Dopamine is an endogenous catecholamine possessing α- and β-adrenergic, and dopaminergic, agonist effects that are dose dependent in nature. Although this agent has gained wide acceptance for its inotropic activity, this effect is reported to be less pronounced in neonates because of age-related differences.[1,2] Dopamine administration also has been shown to result in variable, age-dependent effects on intestinal blood flow. When low-dose dopamine is infused in adult animals, the dopaminergic agonist effects generally are considered to predominate, resulting in renal[3] and mesenteric[3,4] vasodilation. This is in contrast to more variable effects in newborns. Labelled microsphere studies[5] in newborn lambs suggest that dopamine infusion within clinically relevant dose ranges did not selectively vasodilate the mesenteric vascular bed. On the other hand, studies using mesenteric artery flow probes determined that mesenteric resistance decreased over a wide range of dopamine infusion doses in newborn piglets at ages of 1 day, and 2 and 8 weeks, whereas in animals less than 1 day old, there were no changes in resistance. These data suggest that alterations in the response to dopamine may be related partially to maturational or species-dependent differences.

When compared with dopamine, dobutamine has a more selective β-adrenergic effect, a slight α-adrenergic response, and no demonstrable dopaminergic effect in adults.[1] Although studies in infants confirm the efficacy of this agent in improving cardiac output, there exist data to suggest that its α-adrenergic properties are more pronounced in this age group, raising systemic arterial pressure at very low doses.[2,6] Regardless of age, dobutamine would not be expected to increase blood flow to the alimentary tract independent of its effect on cardiac output, because of a lack of dopaminergic properties.[1,7]

Although much is known regarding the hemodynamic responses to dopamine and dobutamine in adults and in term infants, their effects on cardiac function and on organ blood flows in premature infants—who typically take up the majority of neonatal intensive care unit beds—have not been delineated clearly. Having developed a means to obtain prematurely delivered piglets for purposes of acute experimentation, we sought to determine the impact of dopamine and dobutamine infusions on visceral blood flows in neonatal piglets.

METHODS

All experimental procedures were completed within the guidelines and approval of the Institutional Animal Care and Use Committee of the University of South Alabama College of Medicine.

Management of Pregnant Sow

Details regarding the perioperative management of the sow have been detailed elsewhere.[8] Briefly, a pregnant sow was obtained 2 weeks before completion of gestation, determined by breeding dates (based on an average term of 114 days, range 111–116 days). The sow was preanesthetized with intramuscular ketamine (8–10 mg/kg) and xylazine (1–2 mg/kg). Ear veins were cannulated for administration of intravenous fluids and pentobarbital (25 mg/kg) in incremental doses sufficient to secure an operative plane of anesthesia. After controlling the airway via tracheotomy and intubation, the sow was placed on a pressure-cycled ventilator. Anesthesia was maintained with a combination of inhalation (isoflurane, 0.5–0.75%), and intravenous—sufentanil citrate (4–8 μg/kg) and vecuronium bromide (0.05–0.10 mg/kg)—anesthetic agents. Cutdown and cannulation of a foreleg artery was performed to allow continuous monitoring of arterial blood pressure and to obtain samples for blood gases, hematocrits, and additional tests.

The abdomen was entered through a lower midline incision, and the urinary bladder was decompressed with a cystostomy tube. One of the two uterine horns then was exteriorized, and a small incision in the uterine wall was made for the delivery of a piglet. Suture hemostasis of the uterine wall was obtained, the horn was returned to the abdomen, and the incision was covered with sterile, moist towels. The sow was maintained under anesthesia until all piglets (8 to 16 per sow) were delivered, then was killed with an intravenous bolus of saturated potassium chloride.

Preparation of Preterm Piglets

To complete the experiments outlined herein, preterm piglets were obtained from five sows. Care similar to that given in a neonatal intensive care unit was provided to ensure survival of the animals. Immediately after deliv-

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ery, the neonate was towel-dried and placed in a warmed environment. After intramuscular administration of a ketamine (50 mg/kg) and xylazine (1–2 mg/kg) mixture, tracheotomy was performed. Oxygen was administered by a manual resuscitator during transportation of the piglet to the laboratory in which the experiments were undertaken. The piglet was placed on a pressure-cycled ventilator (rate 10–15 breaths per minute, positive pressure 15–25 cm of water, FiO_2 100%). Temperature, monitored continuously by a rectal probe, was maintained at 36 C to 37.5 C with a heat lamp or heating pad.

A cannula was placed in an umbilical vein to administer agents (pentobarbital, 25 mg/kg/hour) necessary to maintain an appropriate plane of anesthesia. Groin cutdown was performed, and a femoral vein was cannulated to provide a port for infusion of dopamine or dobutamine. The ipsilateral femoral artery was cannulated, and the catheter tip was positioned in the abdominal aorta to monitor mean systemic arterial pressure and heart rate, and to obtain blood samples. Through a left thoracotomy, the left atrial appendage was cannulated for injection of microspheres.

Preparation of Term Piglets

Fasted term piglets, obtained at the ages of 1 to 2 and 10 to 14 days, were anesthetized, then underwent tracheotomy and establishment of vascular access in the same manner as the preterm piglets.

Experimental Protocols

Animals were randomly assigned to one of the following treatment protocols: 1) peripheral intravenous infusion of dopamine—preterm (n = 8; × weight = 1050 g), 1- to 2-day-old (n = 9; × weight = 1161 g), and 10- to 14-day-old (n = 8; × weight = 2813 g) piglets; and 2) peripheral intravenous infusion of dobutamine—preterm (n = 8; × weight = 972 g), 1- to 2-day-old (n = 9; × weight = 1244 g), and 10- to 14-day-old (n = 8; × weight = 2238 g) piglets.

After ensuring hemodynamic stabilization of the piglet, the first of four randomly selected radiolabeled microspheres was injected to establish baseline measurements of organ blood flows. In animals randomized to dopamine, a continuous intravenous infusion of the drug (30–120 mg in 100 mL 5% dextrose/water) then was initiated at a dose of 5 μg/kg/minute. The hemodynamic effects of a constant infusion of dopamine appear within 2 minutes of administration, with peak effects noted moments thereafter.[9] A 20-minute equilibration period was allotted at this dose before a second microsphere was injected. The dopamine infusion then was discontinued, and the piglet was allowed a 20-minute recovery time, because it also is known that the half-life of dopamine is 2 minutes and effects of the drug are lost within 10 minutes of discontinuing the infusion.[9,10] The dopamine infusion was reinstituted at a dose of 10 μg/kg/minute, and 20 minutes later, the third microsphere was given. The infusion was discontinued again, and 20 minutes later, the infusion was restarted at a dose of 15 μg/kg/minute; 20 minutes later, the fourth microsphere was injected.

In piglets randomized to receive dobutamine (30–120 mg in 100 mL 5% dextrose/water) therapy, this agent was administered by continuous infusion at the same dose schedule outlined for dopamine. Dobutamine exhibits its peak effect 5 minutes after initiation of a constant infusion, has a half-life of 2 minutes, and loses its hemodynamic effects within 10 minutes of discontinuation of the infusion.[9,11] Therefore, the timetable outlined for dopamine also was followed in these piglets.

In all instances, on completion of the final microsphere injection, the piglet was killed with an intra-atrial bolus of saturated potassium chloride, and the following organs were removed, weighed, and counted for radioactivity: esophagus, stomach, duodenum, small intestine (subdivided into proximal, middle, and distal segments), colon (cecum, proximal, middle, distal, rectosigmoid), pancreas, liver, spleen, kidney, skeletal muscle, skin, heart, and brain. The mucosa from segments of the gastrointestinal tract (esophagus, stomach, small intestine, and colon) was separated from the remaining visceral wall to assess mucosal blood flow distinctively from the underlying muscularis. Blood flow to each organ was determined by the reference organ technique.

Theory

Organ blood flows were measured using 15-μ radiolabeled microspheres. All microspheres (Cerium 141, Strontium 85, Scandium 46, Chromium 51) were injected rapidly through the left atrial cannula while withdrawing blood from the aortic cannula at a constant rate, over a 90-second interval, using a Harvard pump (Harvard Apparatus, South Natick, MA). The order in which the microspheres were infused was randomized. After death and organ harvesting, tissue and blood samples were placed in a LKB gamma counter (LKB 300, Ultrogamma, Sweden), and radioactivity in each tissue sample and from each of the four aortic arterial blood withdrawals was determined and corrected for energy overlap. Blood flow to the various organ samples (Q_T) was calculated for each microsphere injection on a per-gram net weight basis according to the equation

$$Q_T = R_{T \times Q_{ref}}/R_{ref},$$

where R_T and R_{ref} are radioactive counts in the tissue and

Table 1. NEONATAL SYSTEMIC HEMODYNAMIC RESPONSES TO DOPAMINE AND DOBUTAMINE

Treatment	Variable	Dose (μg/kg/min) 0	5	10	15
Term					
Dopamine	HR (bpm)	163.03 ± 8.84	160.24 ± 8.18	199.06 ± 8.75‡	224.94 ± 8.75†‡§
	CO (mL/min)	423.16 ± 55.41	398.52 ± 46.38	429.55 ± 47.44	455.90 ± 60.13
	MAP (mm Hg)	57.29 ± 2.25	55.88 ± 1.83	59.29 ± 1.98	61.88 ± 2.40*§
Dobutamine	HR (bpm)	154.24 ± 6.60	180.35 ± 8.72*	205.76 ± 9.31‡	218.47 ± 8.75†‡§
	CO (mL/min)	418.77 ± 57.27	471.25 ± 65.62	474.59 ± 77.13	497.02 ± 77.55*
	MAP (mm Hg)	51.94 ± 1.63	56.35 ± 2.44	56.12 ± 2.00	58.00 ± 2.35*
Preterm					
Dopamine	HR (bpm)	121.50 ± 7.67	149.25 ± 10.60	194.25 ± 16.07‡	209.75 ± 15.51‡§
	CO (mL/min)	120.02 ± 20.51	142.59 ± 24.97	140.91 ± 31.65	152.15 ± 43.91
	MAP (mm Hg)	46.38 ± 2.82	52.56 ± 3.71	54.50 ± 5.16	52.00 ± 6.29
Dobutamine	HR (bpm)	147.00 ± 10.45	186.00 ± 9.49*	206.25 ± 7.17‡	209.25 ± 7.56‡§
	CO (mL/min)	77.11 ± 16.16	88.69 ± 21.49	82.10 ± 22.33	79.41 ± 20.15
	MAP (mm Hg)	43.00 ± 3.78	49.63 ± 6.18	48.88 ± 5.35	45.38 ± 4.69

* $p < 0.05$ *vs.* 0 μg dose.
† $p < 0.05$ *vs.* 10 μg dose.
‡ $p < 0.0001$ *vs.* 0 μg dose.
§ $p < 0.05$ *vs.* 5 μg dose.

reference blood flow samples, respectively, and Q_{ref} is the withdrawal rate of the aortic arterial blood sample, i.e., the reference organ technique.

Statistical Analysis

Mean response (± 1 SE) was determined for each variable (mean systemic arterial blood pressure, heart rate, cardiac output, and organ blood flows) at 0 (control) 5-, 10-, and 15-μg doses of dopamine or dobutamine. For each agent, within-age group comparisons between doses were analyzed by correlated analysis of variance; between-age group effects at each dose of a given agent were similarly subjected to analysis of variance. Finally, the effects of dopamine were compared with those of dobutamine within age groups. In all instances, whenever a significant F ratio was achieved, both Student's t tests and Newman-Keul's follow-up tests were applied to identify mean differences reaching statistical significance. A p value ≤ 0.05 was accepted as a statistically significant difference.

RESULTS

For each variable monitored, and at each infusion concentration, dopamine produced effects in the 1- to 2-day-old piglets that were not statistically different from those seen in the 2-week-old animals. The same phenomenon occurred in the 1- to 2-day-old and 2-week-old piglet groups given dobutamine. Therefore, for purposes of further analysis, these age groups were combined into one each for dopamine and dobutamine, respectively, hereafter referred to as the "term" groups of piglets.

Systemic Hemodynamic Responses

Within each age group, both dopamine and dobutamine produced moderate dose-dependent increases in heart rate when compared with their respective control (pretreatment) values, although at each infusion concentration, the effect of the two agents on heart rate did not differ appreciably. Despite this uniform chronotropic effect, neither agent appreciably altered the calculated cardiac output in the preterm animals. Although baseline cardiac outputs in term animals were markedly higher than those measured in the preterm piglets, dobutamine alone produced an increase in cardiac output in the older animals—and only at the highest administered infusion concentration. Finally, when compared with their respective baseline values, both dopamine and dobutamine produced equivalent, statistically significant increases in mean systemic arterial pressure in term piglets at the higher (15 μg/kg/minute) infusion dose. In contrast, baseline mean systemic arterial pressures recorded in preterm animals were slightly lower than those of term animals, and were not significantly altered by dopamine or dobutamine at any of the infusion doses administered.

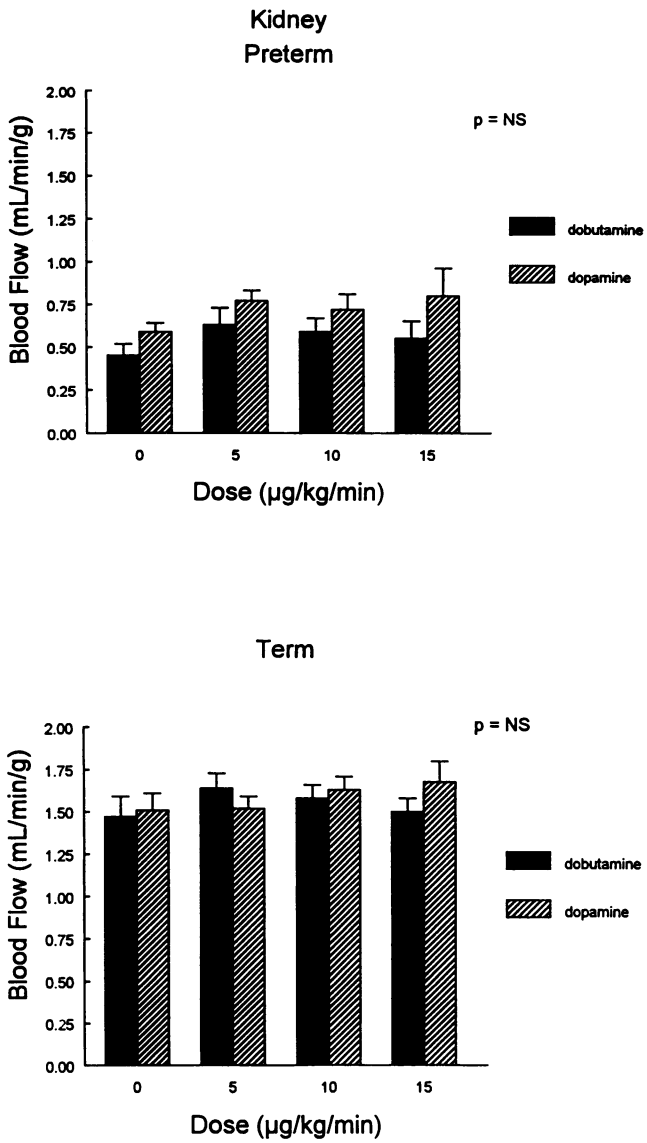

Figure 1. Renal blood flow responses to dopamine and dobutamine in premature and term piglets.

Organ Blood Flows

In general, baseline blood flows to the kidney, heart, and brain were lower in preterm *versus* term piglets, although at each given age group, there were no within-treatment differences in baseline blood flows. Dopamine and dobutamine produced variable effects on blood flows to these organs. For example, in each animal group, the observed increase in renal blood flow in response to either dopamine or dobutamine was statistically insignificant (Fig. 1). In contrast, dopamine generated mild, dose-dependent increases in cardiac (Fig. 2) and cerebral (Fig. 3) blood flow in both premature and term piglet groups, an effect manifested only in the term animals given dobutamine.

In the gastrointestinal tract, baseline blood flows in term animals were uniformly two- to threefold higher than those recorded in the premature piglets, perhaps reflecting minimal blood flow requirements to the "nonworking" (e.g., minimal transport) gut of the unfed prematurely delivered animals. Regardless of these significant baseline differences, both dopamine and dobutamine infusions produced several marked alterations in blood flow to the various portions of the hollow gastrointestinal tract. To illustrate, blood flows to the esophagus and stomach changed little in response to dopamine or dobutamine (Fig. 4). In the premature piglets, esophagogastric blood flow was unaltered by dopamine or dobutamine throughout the range of infusion concentra-

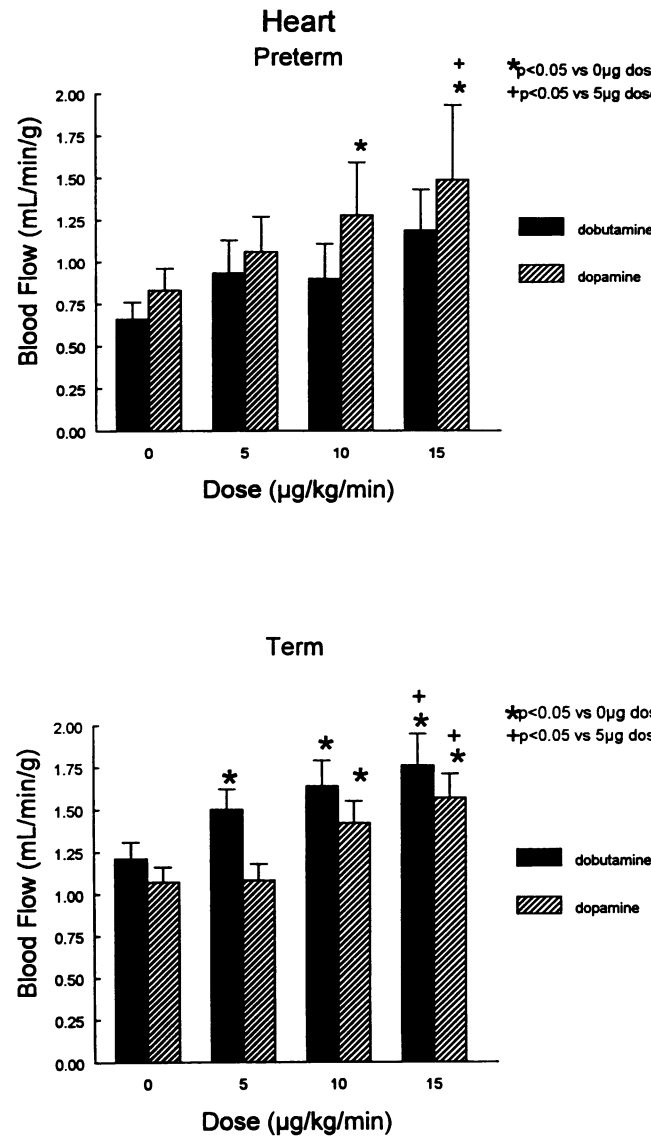

Figure 2. Cardiac blood flow responses to dopamine and dobutamine in premature and term piglets.

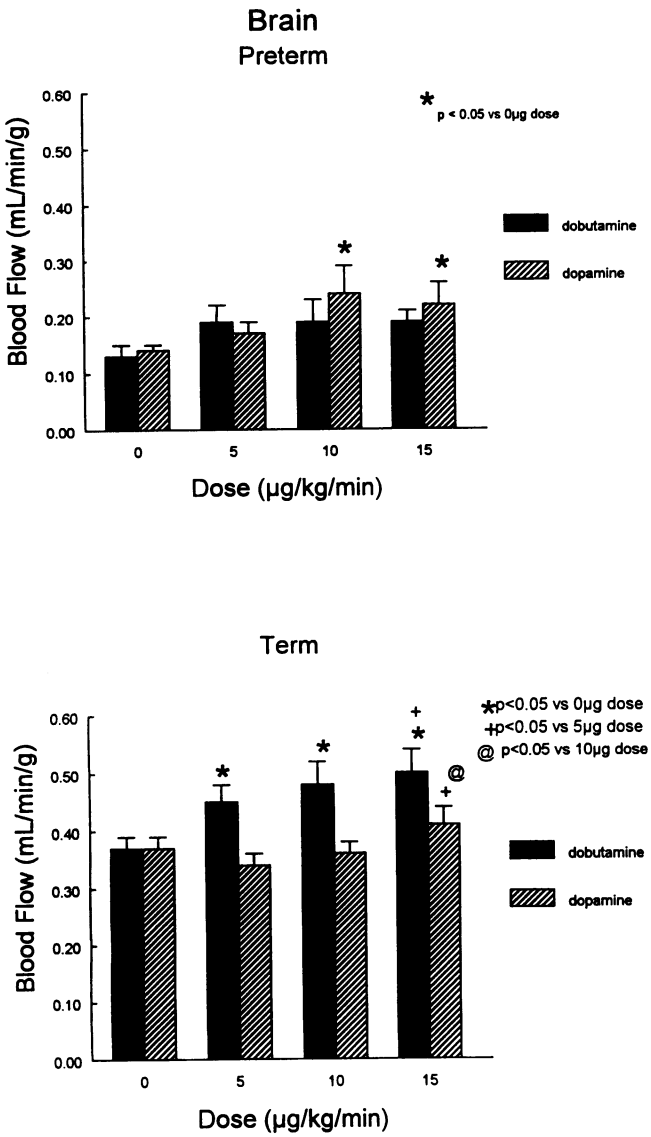

Figure 3. Cerebral blood flow responses to dopamine and dobutamine in premature and term piglets.

tions used; blood flows to these same organs were increased in term animals only by high-dose dopamine, whereas dobutamine produced a mild reduction in blood flow at the highest infusion dose.

In contrast, dopamine effected dramatic and progressive dose-dependent increases in blood flow to the small intestine in both premature and term piglets (Fig. 5)—a phenomenon not observed in either dobutamine-treated group. Hence, when compared with the respective dobutamine-treated groups at the 15-μg/kg/minute infusion rate, dopamine affected a significantly higher blood flow to the small intestine in both preterm and term piglets. The mucosal separation data suggest that the dopamine-induced increases in small intestinal blood flow were distributed evenly between the mucosa (Figs. 6A and 6B) and muscularis (Figs. 6C and 6D) in both age groups.

Similar to the blood flow response pattern observed in the esophagus and stomach, dopamine and dobutamine caused minimal alterations in colonic blood flow (Fig. 7). In premature animals alone, the progressive increase in colonic blood flow reached statistical significance only in dobutamine-treated animals—and solely at the highest infusion concentration. In contrast, colonic blood flow changed little in term animals, although high-dose dopamine did produce a mild decline in colonic blood flow.

DISCUSSION

Beyond confirming the well-documented existence of a dose-related chronotropic response to dopamine and

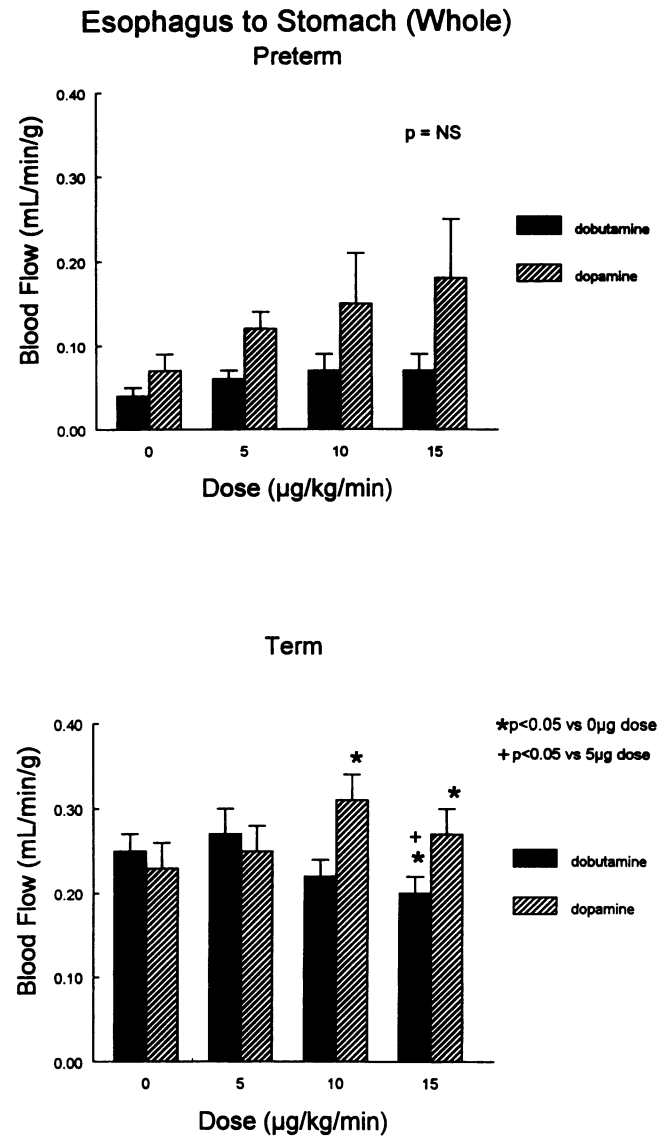

Figure 4. Esophagogastric blood flow responses to dopamine and dobutamine in premature and term piglets.

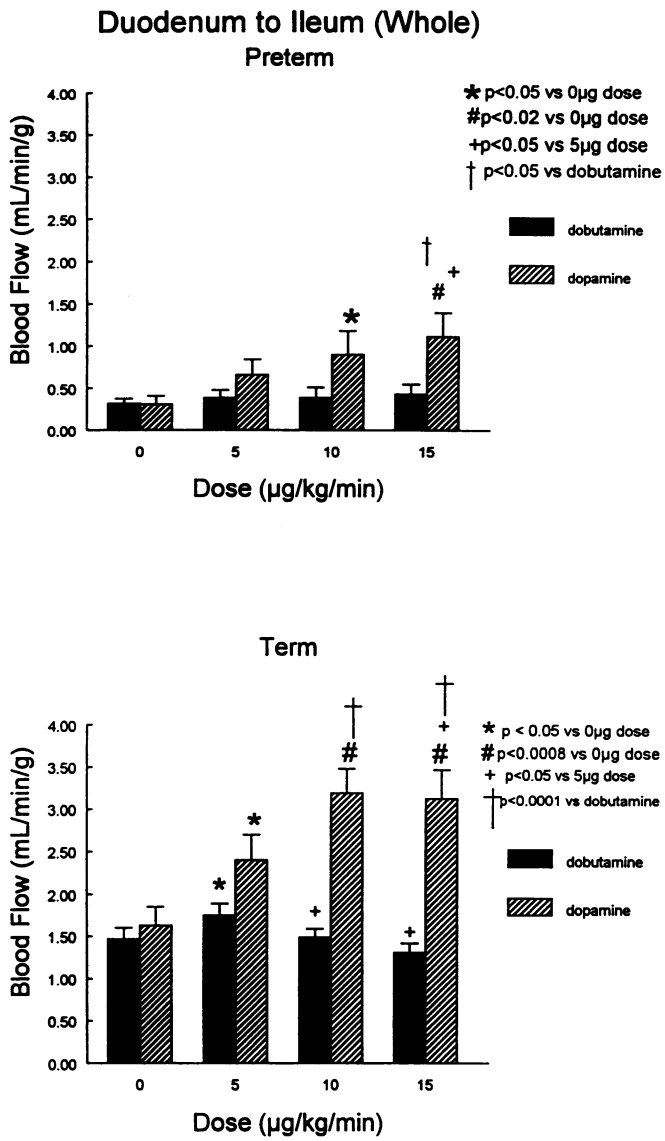

Figure 5. Small intestinal blood flow responses to dopamine and dobutamine in premature and term piglets.

dobutamine in term newborns,[6,7] the data reported in this series document the existence of this reaction to each agent in premature piglets. Therefore, one might have expected dopamine and dobutamine to produce concomitant increases in cardiac output based on the increases in heart rate, particularly because others have found it difficult to increase stroke volume of the immature heart.[12] However, although both dopamine and dobutamine did produce mild increases in calculated cardiac outputs, particularly in the term animal groups, a significant positive inotropic effect was established only with a 15-μg/kg/minute infusion of dobutamine in the term piglets. In contrast, after placing electromagnetic flow probes around the pulmonary artery of newborn piglets to directly measure cardiac output, Nudel et al. observed dramatic positive inotropic effects in response to both dobutamine and dopamine when either was infused at this same concentration.[7] Nudel and associates' technique of directly monitoring cardiac output over time may be more sensitive than the use of injected microspheres to calculate this parameter at all but four points in time during the course of experimentation. This may be a particularly valid interpretation of the data gathered on cardiac outputs in the prematurely delivered piglets, if one assumes that the ductus arteriosus was patent. Because cardiac outputs were calculated from the capture of labelled microspheres in the reference organ (e.g., the timed withdrawal of blood from the aorta) in these experiments, the escape of microspheres into the pulmonary circulation would clearly produce lower-than-expected calculated cardiac outputs in animals that have minute cardiac outputs under baseline conditions, making it all the more difficult to detect specific differences in this variable.

At the 15-μg/kg/minute dose of dopamine, our term animals demonstrated an 8% rise in mean systemic arterial pressure over baseline, an increase that is comparable to the 14% increase reported by others under similar experimental conditions.[7] These findings may be attributed to the enhanced α-adrenergic properties of dopamine at that dose. The increase in mean systemic arterial pressure identified in term animals given dobutamine at this same infusion dose is likely a result of the improved cardiac output documented in this piglet group. The lack of a significant rise in mean systemic arterial pressures with the infusion of either agent in piglets appears at odds with several clinical reports that have found dopamine[2,13,14] and dobutamine[2,14] effective agents to elevate blood pressure in premature infants. However, compared with the normal baseline mean arterial pressures recorded in the premature piglets, pretreatment mean arterial pressures were extremely low in all of the neonates reported in those clinical trials. Moreover, given the critically ill nature of those neonates, the concomitant use of additional resuscitative measures likely influenced these observations. Hence, the 12% mean increase in systemic arterial pressure identified in the relatively "unstressed" premature piglets given dopamine, although not reaching statistical significance, does compare favorably with the 25%- to 35%-increase noted with the use of this agent in clinical trials of critically ill premature infants.

Blood flow to the heart and brain was augmented by dopamine infusions in premature piglets; this contrasts with the absence of any effect on renal blood flow throughout the range of clinically used infusion doses. Previously reported data describing the renal response to dopamine in neonates are controversial. Several investigators have shown that dopamine produced a dose-re-

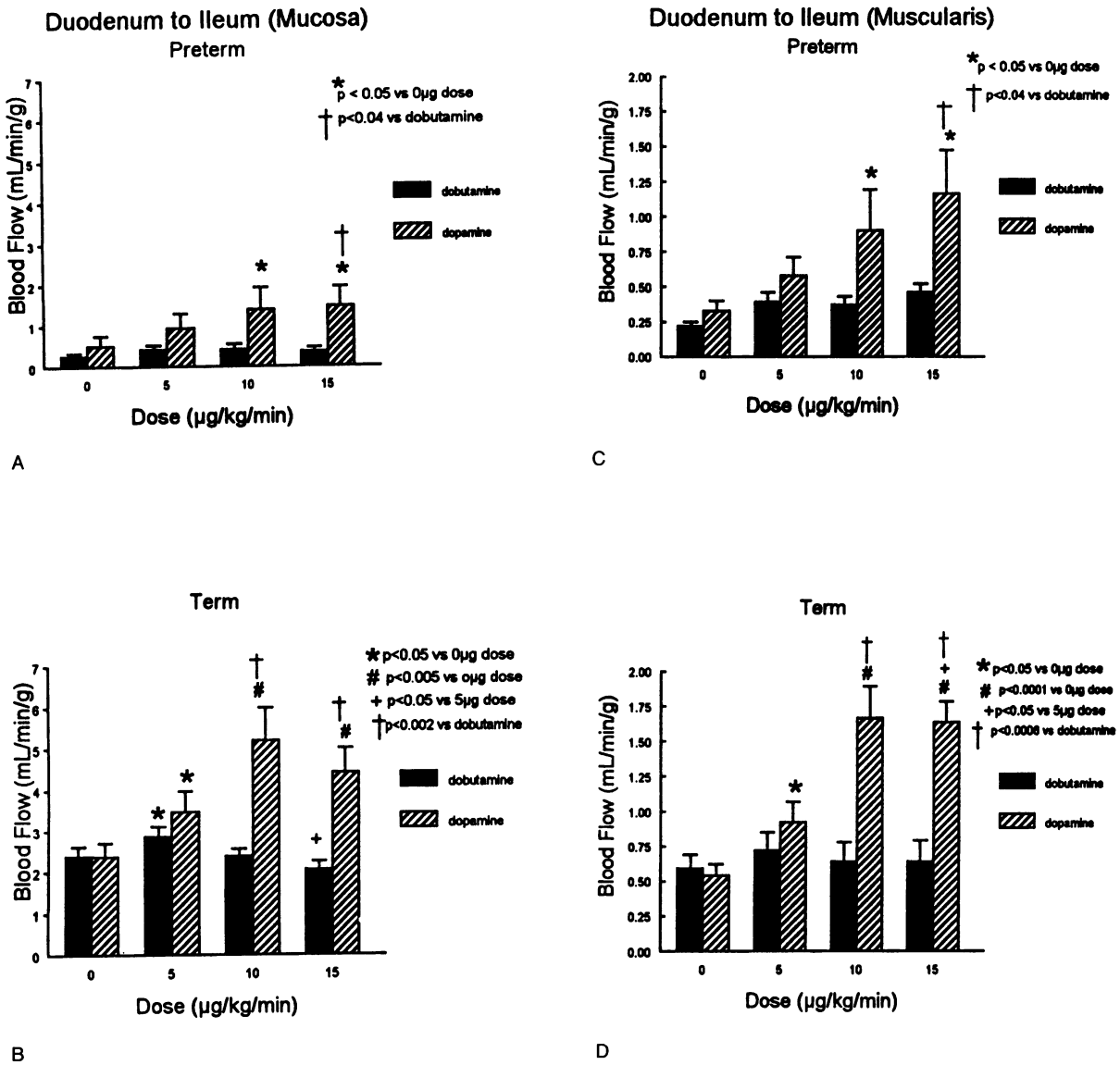

Figure 6. Blood flow responses to dopamine and dobutamine measured in the mucosa (A, B) and muscularis (C, D) layers of the small intestine in premature and term piglets.

lated increase in renal resistance in newborn piglets.[7,15] Similarly, using newborn lambs, Feltes showed that supraclinical doses of dopamine impaired renal blood flow.[5] Driscoll et al., however, demonstrated in newborn dogs that dopamine increased renal blood flow in a dose-related fashion, using concentrations as high as 50 µg/kg/minute.[16] Additional data from fetal sheep experiments indicated that direct infusion of dopamine into the renal artery failed to cause renal vasodilation unless given in the presence of adrenoceptor blockade.[17] Perez et al. have shown that high-dose dopamine infusions in newborns did not alter renal perfusion, indirectly assessed by their finding that urine output was unchanged despite the use of supernormal infusion doses of dopamine.[18] These data are consistent with our data that, in both term newborn and premature piglets, dopamine produces minimal impact on renal blood flow throughout clinically relevant dose ranges.

In this study, the most dramatic dopamine-induced alterations in gastrointestinal blood flow occurred throughout the small intestine of term and premature piglet groups, in which the increased blood flow occurred in a dose-related fashion. These observations differ with the known effects of dopamine infusion in adults, wherein moderate doses of dopamine (up to 10 µg/kg/minute) produce mesenteric vasodilation through dopaminergic receptor activation, whereas higher doses cause mesenteric vasoconstriction mediated by α-adrenocep-

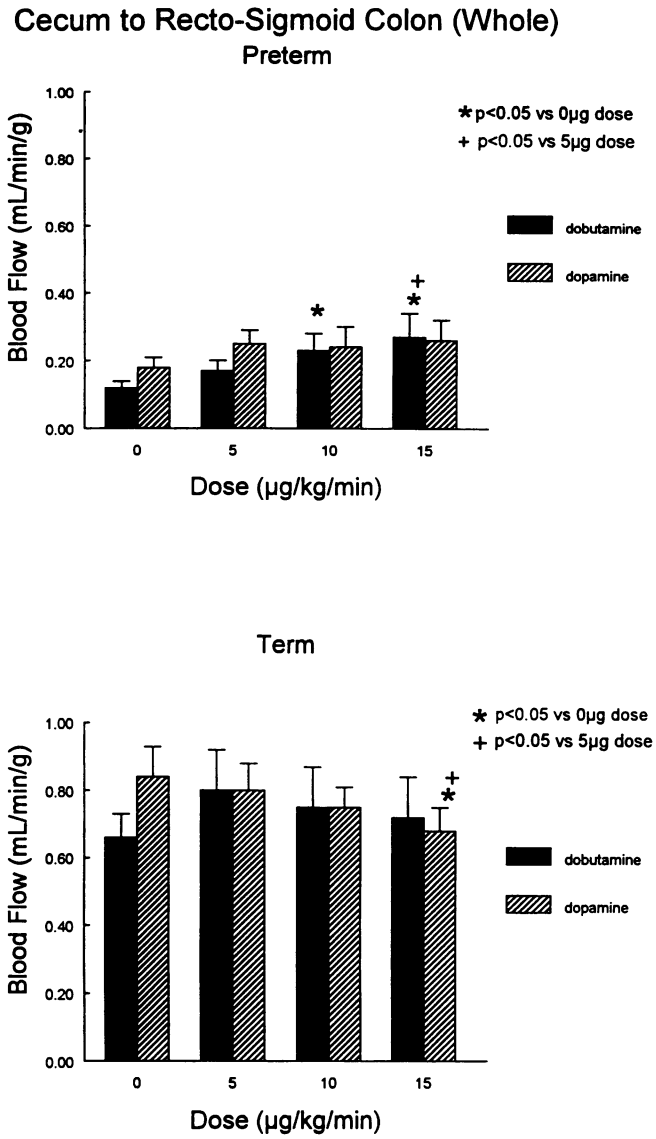

Figure 7. Colonic blood flow responses to dopamine and dobutamine in premature and term piglets.

tors. Other investigators have observed that high-dose dopamine (15 μg/kg/minute) produced mesenteric vasodilation in 2- to 4-day-old and in 2-week-old piglets.[7] Gootman et al., using electromagnetic flow probe techniques, found that mesenteric resistance decreased over a wide range of dopamine doses when infused in 1-day-old, 2-week-old, and 2-month-old piglets.[15] Our data clearly support the dose-response effect of dopamine in term animals, documenting a progressive increase in small intestinal blood flow that nearly doubled at the higher infusion concentration. Dobutamine actually produced a reduction in intestinal blood flow in term piglets; this is consistent with previously reported data in which a 15-μg/kg/minute infusion rate of dobutamine caused an increase in mesenteric vascular resistance in 2-week-old piglets.[7]

Perhaps more importantly, we have shown that small intestinal blood flows measured in prematurely delivered piglets increased in dose-response fashion throughout the range of clinically applicable infusions of dopamine. That intestinal blood flow did not decrease with the higher doses of dopamine in either age group suggests that the α-adrenoceptor population in this particular vascular bed may not be sufficiently developed or functional, leading to persistence of the dopaminergic vasodilator response. We also speculate that, because the three- to fourfold increase over baseline intestinal blood flow at the 15μg/kg/minute dose of dopamine observed in the premature piglets is markedly greater than the twofold increase seen in the term animals given that same dose, maturation of (or lack thereof) the autonomic nervous system relative to the alimentary tract may play a role these observations.

The exact mechanism(s) by which dopamine exerts a dose-response effect on neonatal small intestinal blood flow currently are undefined. Nonetheless, these data may prove particularly salient to the neonatal clinician who, faced with a hypotensive infant, might otherwise be wary of increasing the dopamine dose much beyond 10 μg/kg/minute, fearing a concomitant decrease in mesenteric blood flow—as is known to occur in adults. In addition, our data demonstrated that an increase in neonatal small intestinal blood flow is distributed not only to the muscularis layer, but also to the mucosa, which is felt to be more sensitive to an ischemic challenge. Thus, in clinical scenarios in which a newborn, especially one born prematurely, is placed under conditions that are known to reduce blood flow to the alimentary canal—such as prolonged hypotension, hypoxia, or sepsis—dopamine may prove a valuable adjunctive tool in mitigating the deleterious effects of such insults.

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Discussion

DR. R. NEAL GARRISON (Louisville, Kentucky): Dr. Williams, Secretary Copeland, Members, and Guests. It is a pleasure to discuss Dr. Ferrara and colleagues' work on regional blood flow distribution, a topic of intense interest to me and to Dr. Mark Wilson in our laboratory in Louisville. I thank the authors for providing me with the detailed manuscript in advance of this presentation.

This work is quite extensive and the data have been carefully collected and analyzed and presented this afternoon. It draws attention toward the peripheral microcirculation and away from the central hemodynamic effects of pressor agents, a focus that I think has long been needed.

I would like to focus on one aspect that I feel is most noteworthy about this work, specifically, the effect of dopamine on the distribution of flow to the intestine where the data clearly shows a two- to threefold increase to both muscularis and mucosal flow with the higher doses of dopamine being infused. The authors interpret this to mean, and I think correctly so, that there is a lack of development in the neonatal animal of alpha receptors, i.e., one of the many constrictor forces at work in the adult intestinal microcirculation during stress. If then, during stress, such receptors are not present or inadequately developed, the use of dopamine for the prevention of mucosal ischemia in the neonate should benefit those infants at risk for developing neonatal necrotizing enterocolitis. Would the authors care to speculate on the effectiveness of such treatment during stress where multiple constrictor forces such as endothelin and thromboxane are active? In the adult setting, the constrictor forces are found to be overpowering in comparison to the dilator forces.

Secondly, would they care to speculate on why the absence of these receptors? Are they simply not present in number? Or is there some inadequate development of the metabolic machinery necessary for smooth muscle vasoconstriction?

DR. P. WILLIAM CURRERI (Mobile, Alabama): Dr. Williams, Dr. Copeland, Members, and Guests. It's a real pleasure to comment on this most provocative presentation by Drs. Ferrara, Powell, and colleagues. This study not only confirms others' observations on organ blood flow in newborn animals administered dopamine or dobutamine, but for the first time, reports similar measurements in preterm animals. The importance of these observations cannot be overestimated, since the current sophistication of intensive care technology allows salvage of most premature infants, many of whom are subjected to recurrent hypotensive episodes secondary to a variety of complications during the time required to achieve term weights. Preservation of intestinal blood flow is obviously necessary if the integrity of the hollow viscus organs is to be maintained. The authors should also be commended for an excellent scientific design and appropriate statistical analysis. It should be noted that maintenance of neonatal intensive care standards for the experimental piglets requires enormous commitment in time and resources.

Like all good experimental investigations, this paper stimulates a number of questions which demand further investigation. I have two questions for the authors to address. The authors have noted some disparate responses to dopamine and dobutamine infusion in term animals when different species are studied. Perhaps these discrepancies would also be observed in preterm animals. If so, are the authors confident in suggesting, as they do in their manuscript, that high dose dopamine infusions in human premature infants might be valuable and safe at the present time? These investigators failed to note an increase in cardiac output in their preterm animals following catecholamine infusion despite significant increase in heart rate. They note that others have not been able to increase stroke volume in the immature heart. However, the data that they presented today would suggest a significant decrease in stroke volume. While the authors may be correct that they underestimated cardiac output because of loss of radioactive microspheres through a patent ductus, the alternative explanation that decreased stroke volume occurs following catecholamine infusion with unchanged cardiac output may still be operative. If this is true, organ blood flow must be relatively decreased to other organs not reported here today. What changes in flow were noted in the pancreas, liver, spleen, skeletal muscle and skin, which were also sampled in the course of their study? If flow is markedly decreased to skeletal muscles, this may result in new complications such as respiratory failure.

Again, I congratulate the authors on an innovative study