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Hemodynamic Effects of Epinephrine, Bicarbonate and Calcium in the Early Postnatal Period in a Lamb Model of Single-Ventricle Physiology Created In Utero

V. MOHAN REDDY, MD, JOHN R. LIDDICOAT, MD, DOFF B. McELHINNEY, MS, JEFFREY R. FINEMAN, MD, JUDITH R. KLEIN, MD, ROGER CHANG, FRANK L. HANLEY, MD

San Francisco, California

Objectives. **A reproducible fetal animal model of single-ventricle physiology was created to examine the effects of pharmacologic agents commonly used in the perinatal and perioperative intensive care management of patients with a single ventricle.**

Background. **Single-ventricle physiology is characterized by parallel pulmonary and systemic circulations, with effective blood flow to each determined by the relative resistances in the pulmonary and systemic vascular beds. Perinatal and perioperative management of these patients is largely based on empiric observations and differs considerably between institutions and is further complicated by the transitional physiology of the newborn. The lack of animal models of single-ventricle physiology has hindered the understanding of this problem.**

Methods. **A 10-mm, Damus-Kaye-Stansel–type aortopulmonary anastomosis was created in 10 fetal sheep at 140 ± 1.2 days of gestation. The main pulmonary artery was ligated distally, and pulmonary blood flow (Qp) was provided through a 5-mm aortopulmonary shunt. Eight lambs were delivered at term and placed on cardiopulmonary bypass (30 min) 48 to 72 h after birth. Pharmacologic interventions (0.1 μg/kg body weight per min of epinephrine, 2 mEq/kg of sodium bicarbonate and 10 mg/kg of calcium chloride) were performed before and after bypass, and hemodynamic responses were observed. The response to the epinephrine bolus was determined only in the postbypass study.**

Results. **Both before and after bypass, epinephrine infusion and calcium and bicarbonate administration increased Qp and systemic blood flow (Qs) (total cardiac output) but produced only small changes in the Qp/Qs ratio (−0.5% to −7.3% change). With the epinephrine bolus, Qp increased enormously, and the Qp/Qs ratio increased by 584% ($p < 0.001$).**

Conclusions. **In neonatal lambs with single-ventricle physiology created in utero, epinephrine infusion and calcium and bicarbonate administration increased total cardiac output without significantly compromising the Qp/Qs ratio. However, epinephrine bolus seems to be hemodynamically detrimental in circumstances of single-ventricle physiology and should be used with caution and probably in relatively lower doses in the resuscitation of patients with single-ventricle physiology. Further investigation of the dose-dependent effects and the effects of prolonged administration of common pharmacologic agents will enable better management of patients with single-ventricle physiology.**

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A significant proportion of patients born with congenital heart defects are born with single-ventricle physiology. This includes not only patients with one functional ventricle but also those with two ventricles and nonrestrictive communication at the ventricular or great arterial level. The physiology in these patients is typically characterized by parallel systemic and pulmonary circulations, variable mixing of oxygenated and deoxygenated blood and either excessive or diminished pulmonary blood flow (Qp). Pulmonary and systemic blood flows (Qs) are determined by the relative resistances in the respective vascular beds. The distribution of flow to the pulmonary and systemic circulations affects systemic arterial oxygen saturation and delivery (1). The management of these patients is focused on achieving a critical balance between Qp and Qs to promote adequate systemic oxygen delivery without undue volume overload on the single ventricle. To achieve this critical balance, a variety of ventilatory adjustments and pharmacologic agents are commonly used (1,2). However, considerable controversy exists because decisions are often based on an individual's institutional experiences (3–5), which are often derived from the monitoring of physiologic variables that only indirectly reflect the changes in the systemic pulmonary resistance (SVR) and pulmonary vascular resistance (PVR). In addition, other physiologic effects of altering the PVR/SVR

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Address for correspondence: Dr. V. Mohan Reddy, 505 Parnassus Avenue, M593, San Francisco, California 94143-0118.

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Abbreviations and Acronyms

ANOVA = analysis of variance
CBP = cardiopulmonary bypass
ePTFE = polytetrafluoroethylene
PAP = pulmonary artery pressure
PVR = pulmonary vascular resistance
Qp = pulmonary blood flow
Qs = systemic blood flow
SAP = systemic arterial pressure
SVR = systemic vascular resistance

ratio, such as absolute systemic output, coronary reserve and ventricular mechanics, are often given little importance. The purposes of this study were to establish a reliable fetal animal model of single-ventricle physiology and to study the effects of commonly used pharmacologic agents in the perinatal and perioperative periods.

Methods

Surgical preparation and care. *Ewes and fetuses.* Ten mixed-breed Western ewes (140 ± 1.2 days' gestation, term 145 days) were operated on under sterile conditions with the use of local anesthesia (2% lidocaine hydrochloride), epidural anesthesia (4 ml of 1% tetracaine hydrochloride) and intravenous sedation (50 to 100 mg ketamine hydrochloride). After an 18-gauge angiocath was inserted into the maternal jugular vein, a midline incision was made in the ventral abdomen, and the pregnant horn of the uterus was exposed. Through a small uterine incision, the left fetal forelimb and chest were exposed, and a left lateral thoracotomy was performed in the third intercostal space. Fetal anesthesia consisted of local anesthesia with 1% lidocaine hydrochloride and ketamine hydrochloride (20 mg intramuscularly). Succinylcholine hydrochloride (3 to 5 mg intramuscularly) was administered to prevent fetal breathing movements. The pericardium was incised along the main pulmonary trunk and suspended with tacking sutures (Fig. 1A). The brachiocephalic arterial trunk, ascending aorta and main pulmonary arteries were dissected and controlled with vessel loops (Fig. 1B). A Damus-Kaye-Stansel type of aortopulmonary anastomosis was performed in the following manner: The ascending aorta was side clamped with a side-biting vascular clamp. An aortotomy was performed with a no. 11 bladed knife. The aortotomy was extended to ~10 mm with fine scissors, and a strip of aortic wall was excised to create an oval opening in the ascending aorta. One end of a 5-mm extended polytetrafluoroethylene (ePTFE) vascular graft (W.L. Gore and Associates) was partially anastomosed side to side to the end of a 10-mm ePTFE vascular graft (~10 mm in length) to reduce operative suturing (Fig. 1). These were then anastomosed end to side to the ascending aorta (Fig. 1C). Both anastomoses were performed with 7.0 prolene suture (Ethicon Inc.) using a continuous suture technique. Vascular clips were placed to occlude the grafts temporarily, and the vascular clamp was released gradually to minimize any bleeding at the suture line. A side-biting vascular clamp was then applied to the main pulmonary artery. A pulmonary arteriotomy was performed, and a strip of the posterior pulmonary artery wall was excised. The free end of the 10-mm graft was anastomosed end to side to the opening created in the pulmonary artery. The vascular clamp was gradually released, allowing any air in the graft to escape through the suture line and needle holes. The free end of the 5-mm graft was then anastomosed end to

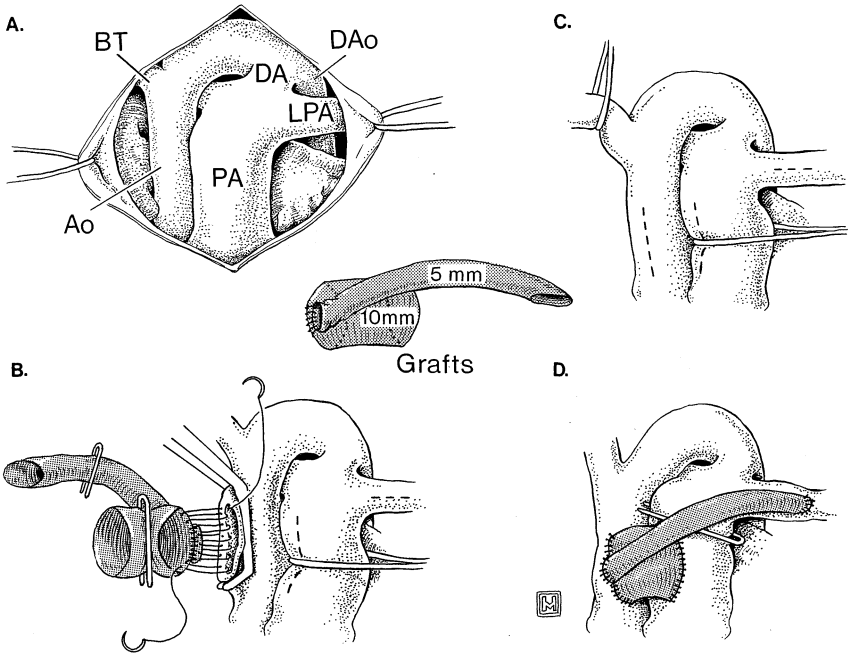

Figure 1. Surgical technique for in utero creation of Damus-Kaye-Stansel anastomosis to achieve single-ventricle physiology. **A,** Surgical exposure and anatomy of the ascending aorta (Ao), descending aorta (DAo), brachiocephalic trunk (BT), ductus arteriosus (DA), main pulmonary artery (PA) and left pulmonary artery (LPA). **B,** Locations of aortotomy and main and left pulmonary arteriotomy incisions, as indicated by the **dotted lines**. **Grafts,** Five- and 10-mm extended polytetrafluoroethylene grafts are connected side to side at the rims to reduce the time required for operative anastomosis. **C,** End to side anastomosis of the 5- and 10-mm grafts to the aortotomy incision with running sutures. **D,** Final appearance of the Damus-Kaye-Stansel anastomosis; clip occlusion of the main pulmonary artery; and 5-mm aorta to left pulmonary artery shunt.

side to an incision made in the left pulmonary artery, providing a source of pulmonary blood flow (Fig. 1D). The vascular clips on the grafts were then removed to establish graft patency. The main pulmonary artery was completely occluded distal to the Damus anastomosis using a large vascular clip. The thoracotomy incision was then closed in layers. Warm saline was infused to replace the lost amniotic fluid, and the uterine incision was closed. After recovery from anesthesia, the ewe was returned to the cage with free access to food and water. Antibiotics (2 million U of penicillin G procaine and 100 mg of gentamicin sulfate) were administered intravenously to the ewe during the operation and daily thereafter for 2 more days.

Lambs. After eight spontaneous deliveries (two fetuses aborted), antibiotics (1 million U of penicillin G procaine and 25 mg of gentamicin sulfate intramuscularly) were administered for 2 days. At 48 to 72 h after birth, eight lambs had 18-gauge polyvinyl catheters placed in an artery and vein of one hind leg under local anesthesia with 1% lidocaine hydrochloride, and the catheters were advanced to the descending aorta and the inferior vena cava, respectively. The lambs were then anesthetized with ketamine hydrochloride (~1 mg/kg body weight per min), intubated with a 4.0-mm (outside diameter) endotracheal tube and mechanically ventilated with a Healthdyne pediatric time-cycled, pressure-limited ventilator (Healthdyne Inc.). Pavulon (pancuronium bromide) was administered by continuous infusion (0.1 mg/kg intravenously). Ventilation with room air (fraction of inspired oxygen 0.21) was adjusted to maintain an arterial partial pressure of carbon dioxide between 35 and 40 mm Hg. A midsternotomy incision was performed and the pericardium was incised. The patent ductus arteriosus was dissected and occluded with a vascular clip. Two single-lumen polyurethane catheters (20 gauge) were inserted, one each, into the left and right atria. A single-lumen polyurethane catheter (20 gauge) was placed in the right pulmonary artery. An ultrasound flow probe (Transonic Systems Inc.) was placed around the 5-mm graft (shunt) to continuously monitor Qp. Ultrasound flow probes were also placed on the brachiocephalic trunk and the aortic arch for continuous monitoring of Qs.

Measurements. Pulmonary and systemic arterial and right and left atrial pressures were measured using Statham P23Db pressure transducers (Statham Instruments, Hato Rey, PR). Mean pressures were obtained by electrical integration. Heart rate was measured by a cardiotachometer triggered from the phasic systemic arterial pressure pulse wave. Qp and Qs were measured with an ultrasound flow meter (Transonic Systems Inc.). All hemodynamic variables were continuously recorded on a Gould multichannel electrostatic recorder (Gould Inc.). Blood gases and pH were measured by a Corning 158 pH/blood gas analyzer (Corning Medical and Scientific). Hemoglobin concentration and oxygen saturation were measured by a hemoximeter (model OSM 2, Radiometer, Copenhagen, Denmark). PVR and SVR were calculated using standard formulas. Total cardiac output is calculated as the sum of Qs and Qp (coronary blood flow is not accounted for with this technique using flow probes).

Experimental protocol. *Hemodynamic study.* After a 30-min recovery period after instrumentation baseline measurements of the hemodynamic variables—pulmonary and systemic arterial pressure, left and right atrial pressures, heart rate, Qp and Qs—systemic arterial blood gases were obtained. The following pharmacologic agents were then administered in random order and their effects were noted. Sodium bicarbonate ("bicarbonate"; 2 mEq/kg) was administered into the right atrium as a bolus given over 1 min. The hemodynamic variables were measured continuously. The maximal hemodynamic effects after bicarbonate administration, which generally occurred within 2 min, were recorded as the postbicarbonate infusion values. Systemic arterial blood gases and pH were measured at the same time. After a 30-min recovery period, all measurements were repeated and calcium chloride ("calcium"; 10 mg/kg) was administered into the right atrium as a bolus given over 1 min. Hemodynamic variables were measured continuously. Maximal hemodynamic effects after calcium administration, which generally occurred within 2 min, were recorded for analysis as the postcalcium infusion values. Systemic arterial blood gases and pH were also checked simultaneously. After 30 min, all measurements were obtained again, and epinephrine infusion was started at 0.1 μg/kg per min in the right atrium. After 10 min a new steady state was achieved and all the measurements were repeated and recorded as postepinephrine infusion values. Epinephrine infusion was stopped, and after a waiting period of 30 min, all measurements were repeated and the lambs were placed on cardiopulmonary bypass (CPB). On CPB the lambs were cooled to 15°C, and circulatory arrest was established for 30 min to mimic a stage I Norwood procedure. The lambs were then rewarmed fully and removed from CPB. After a 60-minute recovery period, all hemodynamic measurements, systemic arterial blood gases and pH levels were obtained and a stable state was established. The interventions (bicarbonate, calcium and epinephrine infusion in random order) were repeated, and preinfusion and postinfusion values were recorded in the same manner as before bypass. In addition, after hemodynamic values were recorded and systemic arterial blood gases and pH were measured to assess hemodynamic stability, an epinephrine bolus (0.05 ml/kg, 1:10,000 vol) was administered as the last intervention. Hemodynamic variables were continuously monitored and systemic arterial blood gases were checked 5 min after the bolus. The maximal effects, which generally occurred soon after administration, were recorded for analysis as postepinephrine bolus values. At the end of the study, the lambs were given a lethal dose of pentobarbital sodium. An autopsy was performed to confirm the placement of intravascular catheters and shunt patency.

The experimental protocol was approved by the Committee on Animal Research of the University of California, San Francisco. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society of Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the

Table 1. Prebypass and Postbypass Hemodynamic Measurements Before and After Epinephrine Infusion and Administration of Bicarbonate and Calcium

Intervention	PAP (mm Hg)	SAP (mm Hg)	Qp (ml/min per kg body weight)	Qs (ml/min per kg body weight)	Qp:Qs	PVR (mm Hg/ml per min per kg)	SVR (mm Hg/ml per min per kg)
Epinephrine (epi)							
Before bypass							
Pre-epi	29.0 ± 7.4	59.5 ± 12.4	262 ± 40	145 ± 35	1.93 ± 0.69	0.088 ± 0.026	0.39 ± 0.14
Post-epi	31.3 ± 6.0*	64.3 ± 12.4†	298 ± 56‡	173 ± 38§	1.82 ± 0.64	0.085 ± 0.020	0.35 ± 0.11
After bypass							
Pre-epi	28.6 ± 6.0	50.9 ± 9.9	238 ± 60	171 ± 46	1.48 ± 0.54	0.098 ± 0.025	0.28 ± 0.13
Post-epi	29.7 ± 5.6	57.1 ± 8.8†	267 ± 54‡	195 ± 49†	1.47 ± 0.55	0.091 ± 0.019*	0.28 ± 0.11
Sodium bicarbonate (bicarb)							
Before bypass							
Pre-bicarb	32.3 ± 5.6	60.0 ± 9.7	252 ± 46	131 ± 28	2.04 ± 0.80	0.106 ± 0.032	0.44 ± 0.13
Post-bicarb	32.6 ± 5.5	66.9 ± 14.0*	276 ± 59*	149 ± 36‖	2.02 ± 1.0	0.093 ± 0.027*	0.44 ± 0.17
After bypass							
Pre-bicarb	28.9 ± 4.0	52.7 ± 10.4	237 ± 62	165 ± 45	1.55 ± 0.64	0.103 ± 0.026	0.31 ± 0.15
Post-bicarb	29.1 ± 4.6	56.3 ± 11.7‖	260 ± 61§	191 ± 48§	1.45 ± 0.47*	0.083 ± 0.020†	0.28 ± 0.13*
Calcium chloride (calcium)							
Before bypass							
Pre-calcium	31.7 ± 5.4	55.5 ± 11.6	249 ± 30	130 ± 39	2.09 ± 0.80	0.108 ± 0.031	0.41 ± 0.15
Post-calcium	32.0 ± 5.4	59.0 ± 12.5†	268 ± 26†	150 ± 41§	1.90 ± 0.58*	0.100 ± 0.025	0.38 ± 0.14*
After bypass							
Pre-calcium	28.6 ± 4.4	51.7 ± 8.8	238 ± 55	149 ± 49	1.71 ± 0.55	0.101 ± 0.027	0.34 ± 0.14
Post-calcium	28.9 ± 4.0	58.0 ± 7.8*	268 ± 62†	174 ± 50§	1.60 ± 0.44	0.090 ± 0.025†	0.32 ± 0.11

*$p < 0.05$, †$p < 0.001$, ‡$p < 0.005$, §$p < 0.0001$, ‖$p < 0.01$, relative to preadministration values. Data presented are mean values ± SD. PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; Qp = indexed pulmonary blood flow; Qp/Qs = pulmonary/systemic blood flow ratio; Qs = indexed systemic blood flow; SAP = systemic arterial pressure; SVR = systemic vascular resistance.

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Statistical analysis. Data are expressed as mean value ± SD. The significance of changes in hemodynamic variables produced by drug administration was analyzed by the paired two-tailed *t* test. Comparisons between drugs and before and after bypass for each variable were made using repeated measures analysis of variance (ANOVA) for the seven surviving animals. The post hoc test used was the Student-Newman-Keuls test. Unless stated otherwise, interaction terms were not significant. For analysis of the hemodynamic effects of epinephrine bolus, which was administered only after bypass, the paired two-tailed *t* test was performed. SPSS for Windows version 6.0 (SPSS Inc.) was used for all statistical analyses. Values of $p \leq 0.05$ were considered significant.

Results

All animals remained hemodynamically stable during prebypass study, and hemodynamic data were obtained and analyzed in all eight animals. However, during bypass, the study was discontinued in one animal owing to accidental massive air embolism. The other seven animals were hemodynamically stable throughout the bypass and postbypass periods, and hemodynamic data were available for all seven animals. Prebypass changes after infusion of epinephrine, bicarbonate and calcium were calculated from the data for all eight animals, whereas postbypass statistics reflect data for the seven surviving animals. Repeated measures ANOVA was performed using only the seven surviving animals. Prebypass and postbypass hemodynamic data in response to epinephrine infusion, bicarbonate and calcium are summarized in Table 1. Hemodynamic responses to epinephrine bolus after bypass are depicted in Figure 2.

Pulmonary artery pressure (PAP). Epinephrine infusion before bypass resulted in a significant rise in PAP. Epinephrine infusion after bypass led to an insignificant rise in PAP. Bicarbonate and calcium administration led to small, insignificant rises in PAP both before and after bypass. An epinephrine bolus after bypass produced a 76% increase in PAP ($p < 0.0001$).

Systemic arterial pressure (SAP). The effects on SAP of prebypass and postbypass epinephrine infusion, bicarbonate and calcium are shown in Figure 3. Both before and after bypass, epinephrine infusion, bicarbonate and calcium produced significant increases in SAP. The postbypass increase was greater for epinephrine and calcium and less pronounced for bicarbonate, but none of these differences were significant. Repeated measures ANOVA interactions approached significance ($p = 0.08$). The postbypass epinephrine bolus resulted in a sudden and significant 152% increase in SAP ($p < 0.0001$).

Indexed pulmonary blood flow. Prebypass and postbypass effects of epinephrine infusion, bicarbonate and calcium on Qp are shown in Figure 4. Epinephrine infusion, bicarbonate and

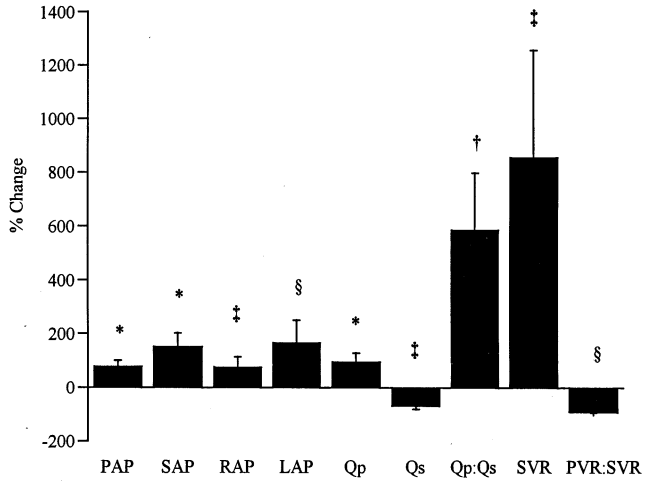


Figure 2. Mean (±SD) percent change from baseline in PAP, SAP, left atrial pressure (LAP), right atrial pressure (RAP), indexed Qp, indexed Qs, Qp/Qs ratio, SVR and PVR/SVR ratio after postbypass epinephrine bolus injection. *p < 0.0001; †p < 0.001; ‡p < 0.0005; §p < 0.005.

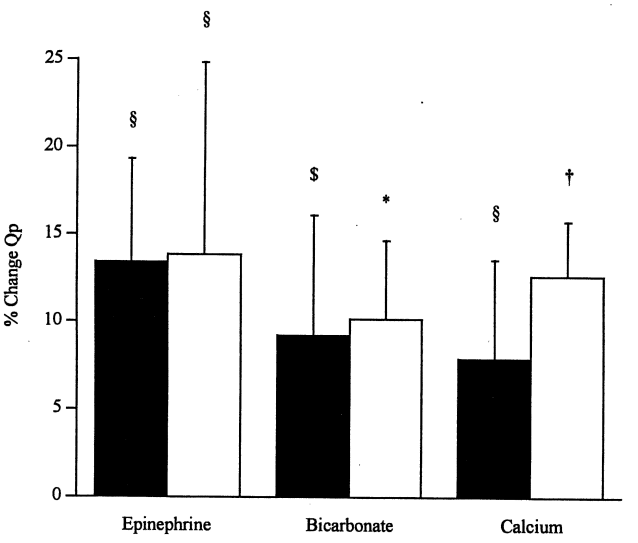


Figure 4. Mean (±SD) percent change in indexed Qp after epinephrine infusion and administration of bicarbonate and calcium before (n = 8 [**solid bars**]) and after (n = 7 [**open bars**]) CPB. §p < 0.005; $p < 0.05; *p < 0.0001; †p < 0.001.

calcium all led to significant increases in Qp both before and after bypass. Notably, the postbypass effect of calcium was significantly greater than the prebypass effect. Repeated measures ANOVA interactions approached significance (p = 0.09). The epinephrine bolus after bypass increased Qp by 94% (p < 0.0001).

Indexed systemic blood flow. Prebypass and postbypass effects of epinephrine infusion, bicarbonate and calcium on Qs are depicted in Figure 5. Epinephrine infusion, bicarbonate and calcium all produced significant rises in Qs before and after bypass. The prebypass and postbypass effects did not differ significantly for any of these agents. Systemic blood flow fell significantly after the postbypass epinephrine bolus (p < 0.0005).

Pulmonary/systemic blood flow ratio (Qp/Qs). The Qp/Qs ratio decreased slightly after prebypass and postbypass epinephrine infusion, bicarbonate and calcium. Only in the case of postbypass bicarbonate administration was this decrease significant. The postbypass epinephrine bolus produced an increase of 584% in Qp:Qs (p < 0.001).

Pulmonary vascular resistance. Epinephrine infusion, bicarbonate and calcium all produced insignificant decreases in PVR before bypass and significant decreases in PVR after bypass. The difference between prebypass and postbypass

Figure 3. Mean (±SD) percent change in SAP after epinephrine infusion and administration of bicarbonate and calcium before (n = 8 [**solid bars**]) and after (n = 7 [**open bars**]) CBP. †p < 0.001; $p < 0.05; ‡p < 0.01; §p < 0.005.

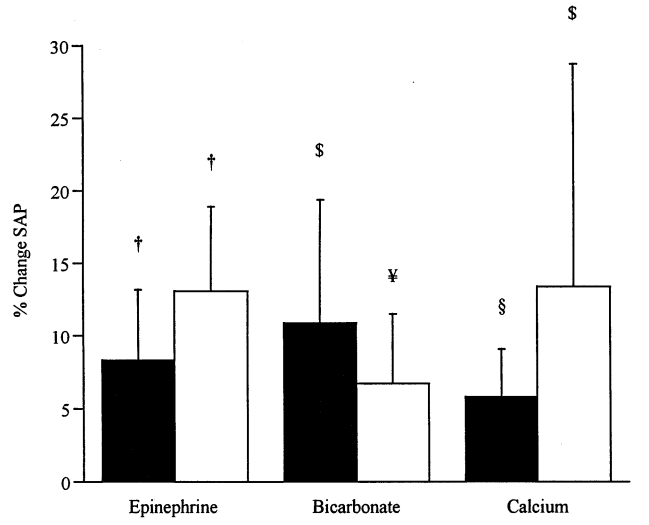
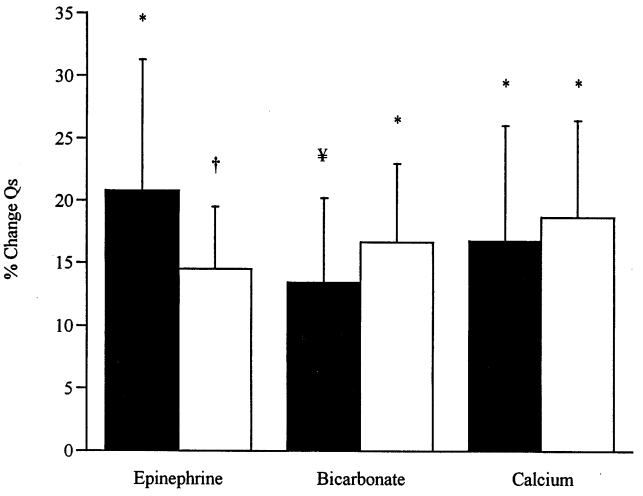


Figure 5. Mean (±SD) percent change in indexed Qs after epinephrine infusion and administration of bicarbonate and calcium before (n = 8 [**solid bars**]) and after (n = 7 [**open bars**]) CPB. *p < 0.0001; †p < 0.001; ‡p < 0.01.



changes was not significant with any of these agents. Epinephrine bolus after bypass lowered PVR by 18% ($p = 0.028$).

Systemic vascular resistance. Prebypass and postbypass epinephrine infusion led to an insignificant decrease in SVR. The SVR changed negligibly after prebypass bicarbonate administration, but decreased significantly after postbypass bicarbonate. Calcium produced a significant decrease in SVR before bypass and an insignificant decrease in SVR after bypass. The epinephrine bolus after bypass increased SVR by 856% ($p < 0.0005$).

Discussion

Background. Infants born with congenital heart defects that result in functional single-ventricle physiology are often difficult to manage in the neonatal and postoperative periods. Congenital anomalies characterized by single ventricle physiology, which include a single right ventricle, a single left ventricle, tricuspid atresia, a double-outlet right ventricle and hypoplastic left heart syndrome, share the common trait of *pulmonary and systemic circulations that are perfused in parallel rather than in series*. The balance between Qp and Qs in such circumstances depends primarily on the relative resistances in the pulmonary and systemic vascular beds (1). The absolute and relative volumes of Qp and Qs, in turn, determine the clinical presentation of various single ventricle types of congenital heart defects. If Qp is markedly increased, systemic hypoperfusion and metabolic acidosis develop, whereas reduced Qp results in hypoxemia and cyanosis despite adequate systemic perfusion. Increased Qp in certain subgroups of neonates can also lead to a progressive volume overload on the single ventricle, congestive heart failure and elevation in PVR. Thus, a careful balance between Qp and Qs must be maintained to preserve sufficient arterial oxygen saturation without overloading the single ventricle (1,2). Imbalance in either direction can be lethal, especially during times when these resistances are typically in flux.

Two specific settings in which the pulmonary and systemic resistance beds change dramatically are during the period of early neonatal transitional physiology and after CPB used during surgical palliation for these infants. Various respiratory and pharmacologic interventions are often used in efforts to achieve a critical balance between Qp and Qs. Management approaches to these patients are controversial and vary considerably from one institution to another, largely on the basis of experience and empiric observations (2–5). The infant, meanwhile, remains a physiologic "black box."

Very few experimental studies have been carried out to substantiate or refute the current clinical practices. One experimental study (6) has yielded important information. However, the model employed was created acutely and beyond the period of transitional physiology, which means that the animals studied had normal cardiovascular physiology for a period of time before surgical creation of single ventricle physiology. Other investigators (7) have reported a mathetical model that is based on numerous assumptions. Although these studies have and may continue to provide important information, the fact that they were created acutely and beyond the period of transitional physiology must be seen as an important inherent limitation. The present model, in contrast, is created in utero, and is therefore not an acutely stressed model. In addition, the single-ventricle physiology is present from the time of birth, unlike previous models, which had a period of normal circulation for a few weeks.

Findings with a new experimental model. Although the cardiac and vascular effects of epinephrine, bicarbonate and calcium are well known in the normal circulation (8–10), there is no information on the hemodynamic effects of these pharmacologic interventions in the setting of single-ventricle physiology. In the present study, the hemodynamic effects of pharmacologic agents commonly used in the critical care setting were evaluated in the early neonatal period and after CPB. As anticipated, epinephrine infusion increased cardiac output, resulting in rises in absolute Qp and Qs. However, the Qp/Qs ratio did not change significantly before or after bypass. Calculated SVR and PVR decreased with epinephrine infusion. The decrease in SVR is consistent with the fact that epinephrine in low doses acts predominantly on $beta_2$ receptors and dilates the skeletal muscle vasculature. However, the changes in calculated SVR and PVR may, in part, be due to the increase in Qp and Qs from the positive inotropic effect of epinephrine (9,10). Epinephrine infusion does not appear to cause any major imbalance in the Qp/Qs ratio, but further studies are needed to clarify its dose-dependent effects.

Sodium bicarbonate administration also increased the absolute Qp and Qs and decreased PVR and SVR both before and after bypass, with minor changes in the Qp/Qs ratio. The changes produced by bicarbonate are probably due to the direct effects on the vascular smooth muscle in response to the pH alteration. The effects of calcium were similar to bicarbonate, but are more likely due to increased cardiac output from the positive inotropic effect of calcium on the ventricular muscle. Further evaluation of dose-responsive hemodynamic effects of calcium and bicarbonate will be of importance in the management of patients with single-ventricle physiology.

The finding of most concern in this study is the massive increase in SVR and the tremendous increase in Qp resulting from the epinephrine bolus. The extreme imbalance in the Qp/Qs ratio (Fig. 2), caused by even half the code dose (we gave 0.05 ml/kg) of epinephrine, suggests that boluses of epinephrine should be used cautiously and in reduced amounts in the management of patients with single-ventricle physiology.

Study limitations. The present model has two drawbacks: 1) There are two ventricles pumping into the aorta. 2) Mixing occurs in the aorta, thereby resulting in streaming. Nevertheless, the strength of the model lies in the fact that the most important feature of single-ventricle physiology, namely, parallel systemic and pulmonary circulations with shunt-dependent Qp, is present from birth.

Another critique of this study is that all pharmacologic interventions were performed in stable animals. This is unre-

alistic from a clinical point of view, because the pharmacologic interventions studied are only performed in unstable patients or in those who have a low cardiac output, or when there is an imbalance of Qp and Qs. However, the data from this study provide useful information on commonly used pharmacologic agents.

Conclusions. This fetal-neonatal model closely mimics the single ventricle physiology seen in neonates born with various commonly occurring lesions. An adequate understanding of single-ventricle physiology during the transitional phase of circulation has great relevance to the management of many neonates with congenital heart defects, who almost always need therapeutic intervention during the first few hours to few days of life. Therefore, this model provides a tool for investigating the mechanisms behind hemodynamic changes during the transitional phase and perioperative period, and allows for the evaluation of various means of manipulating PVR and SVR to achieve a critical balance between Qp and Qs. Epinephrine infusion and calcium and bicarbonate administration increase total cardiac output without a significant change in the Qp/Qs ratio. However, an epinephrine bolus appears to be hemodynamically detrimental in circumstances of single ventricle physiology. An epinephrine bolus should be used with caution in the resuscitation of patients with single-ventricle physiology and probably in smaller doses than usual in patients with normal circulation. Further investigation to study the dose-dependent effects as well as the effects of prolonged administration of common pharmacologic agents used in the management of patients with single-ventricle physiology is warranted.

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