Effects of single-ventricle physiology with aortopulmonary shunt on regional myocardial blood flow in a piglet model

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Supplemental material is available online.

Objectives: In single-ventricle physiology with aortopulmonary connection, diastolic hypotension could alter regional myocardial blood flow. Also, afterload increases could impair myocardial blood flow by increased wall tension and relative subendocardial malperfusion. This study explores the effects of acute single-ventricle physiology on regional myocardial blood flow distribution and investigates the consequences of moderate afterload augmentation on myocardial blood flow.

Methods: Single-ventricle physiology was created in 8 piglets without using bypass, and 8 animals served as a sham control group. Aortopulmonary shunt, echo-guided atrial septostomy, tricuspid valve avulsion, and pulmonary artery occlusion allowed the left ventricle to support systemic and pulmonary circulations. Afterload augmentation was produced by aortic balloon inflation. Physiologic recordings and stable-isotope microsphere determination of myocardial blood flow to the subepicardium and subendocardium were obtained at baseline and during single-ventricle physiology (at 30 minutes, 120 minutes, and afterload increase).

Results: Arterial oxygen content, diastolic pressure, and coronary perfusion pressure declined after creation of single-ventricle physiology ($P < .05$). Acute single-ventricle physiology resulted in higher myocardial blood flow ($P < .05$), unchanged subendocardial/subepicardial flow ratio and oxygen delivery, and lower coronary resistance ($P < .01$) as compared with biventricular physiology. Afterload augmentation increased coronary perfusion pressure, causing a trend for higher myocardial blood flow and oxygen delivery ($P = \text{NS}$), without affecting subendocardial/subepicardial flow distribution. Myocardial oxygen supply/demand balance fell in single-ventricle physiology, remaining unchanged during afterload augmentation.

Conclusions: Our study demonstrates that, in acute single-ventricle physiology with aortopulmonary shunt, myocardial blood flow is maintained by lower coronary perfusion pressure. Further, single-ventricle physiology results in less favorable myocardial oxygen supply/demand balance, although normal transmural myocardial blood flow distribution is maintained. Avoidance of diastolic runoff (ventricle-pulmonary conduit) could improve coronary reserve. In our study, moderate afterload augmentation did not induce relative subendocardial malperfusion, nor did it worsen oxygen supply/demand balance.

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Univentricular physiology with aortopulmonary connection is associated with an increased risk of myocardial ischemia.¹⁻³ Coronary flow may be compromised by diastolic runoff through the systemic-pulmonary shunt, with consequently lower diastolic pressure and coronary perfusion pressure

Abbreviations and Acronyms

Cao ₂	= arterial oxygen content
CPP	= coronary perfusion pressure
LV	= left ventricle/ventricular
MBF	= myocardial blood flow
NS	= not significant
RPP	= rate-pressure product
SVP	= single ventricle physiology
SVR	= systemic vascular resistance

(CPP).^{4,5} Hypoxemia, increased volume load, and unbalanced pulmonary-systemic flow distribution may contribute to adversely affect the myocardial oxygen supply/demand relationship.^{4,5}

Acute myocardial ischemia is a known cause of sudden death early and late after palliation of human single-ventricle physiology (SVP).⁶ Changes in systemic vascular resistance (SVR) have been proposed as a potential mechanism for myocardial ischemia and reduced ventricular function. In SVP, a sudden decline in SVR can result in inadequate coronary perfusion.^{5,6} Sudden increases in SVR have also been proposed as a cause of unexpected cardiovascular collapse, although the mechanism remains unclear.⁷ Higher SVR could abruptly increase ventricular wall tension, worsening myocardial supply/demand equilibrium.⁸ Further, it could alter transmural myocardial blood flow (MBF) distribution, resulting in relative subendocardial malperfusion.⁸ However, higher SVR could also increase CPPs, thereby promoting coronary flow.

MBF is difficult to investigate in SVP, clinically or experimentally, owing to the need for invasive measurements and the challenges of animal models. To date, there are no experimental studies on myocardial perfusion in SVP, and data from clinical studies are limited.^{3,9} The consequences of SVP on regional MBF distribution and oxygen delivery have been incompletely characterized. Further, the effect of afterload increases on MBF is unknown. As a result, we studied MBF and myocardial oxygen delivery in an acute piglet model of SVP, and we investigated the consequences of afterload augmentation on regional MBF distribution.

Methods**Animals**

Newborn Yorkshire piglets weighing 3.7 ± 0.4 kg were used. The study was approved by the Animal Care and Use Committee of the University of Miami and was carried out in compliance with the 1996 National Research Council guidelines for the Care and Use of Laboratory Animals (National Institutes of Health publication No. 85-23, revised 1985).

Surgical Preparation

Piglets were anesthetized with intramuscular ketamine (40 mg/kg) and xylazine (4 mg/kg), intubated via tracheostomy, and placed on volume-controlled ventilation (tidal volume 25-30 mL/kg, rate 25 breaths/min, inspired oxygen fraction 25%). Anesthesia was maintained with continuous infusion of fentanyl ($50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), pancuronium ($0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), and midazolam ($0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). A catheter was inserted in the femoral artery for pressure monitoring and blood sampling. A 6F introducer sheath was inserted in the opposite femoral artery and used for intra-aortic balloon inflation (afterload augmentation). A 7F introducer sheath was placed in the femoral vein for fluid administration and subsequent insertion of an atrial septostomy catheter. The electrocardiogram and rectal temperature were monitored.

The SVP model resembled that described previously by others.^{10,11} Through a sternotomy, catheters were placed in the right and left atria. Heparin was given (150 units/kg), and a 3.5-mm polytetrafluoroethylene shunt (Gore-Tex shunt; W. L. Gore & Associates, Inc, Flagstaff, Ariz) was interposed between the aorta (proximal to the takeoff of the innominate artery) and the pulmonary artery. The shunt was initially kept clamped, while a 2-mL balloon septostomy catheter (Medtronic Vascular, Danvers, Mass) was advanced from the right femoral vein into the right atrium. Epicardial 2-dimensional echocardiography was used to perform a pullback septostomy. The same catheter was then advanced into the right ventricle. The tricuspid valve was made incompetent by repeatedly withdrawing the inflated balloon across the valve. Last, the shunt was opened, and the main pulmonary artery was occluded. This allowed the left ventricle (LV) to support both systemic and pulmonary circulations, reproducing a physiology similar to that of pulmonary atresia with intact ventricular septum (Figure E1).^{10,11} In this model, avulsion of the tricuspid valve is necessary to prevent right ventricular distention.¹⁰⁻¹² The adequacy of the atrial septostomy was confirmed by epicardial echocardiography (Figure E1). Afterload augmentation was produced by balloon inflation in the distal descending thoracic aorta for 15 minutes to completely occlude the aortic lumen.

Animals treated as sham controls received identical preparation, but were kept in a biventricular state. A shunt was constructed by use of similar surgical maneuvers, and clamped. The atrial septostomy and tricuspid valve avulsion were simulated by manipulating the catheter against or across the atrial septum and tricuspid valve, without inflating the balloon.

Experimental Protocol

Eight piglets were included in the SVP group, and 8 were treated as sham-operated controls. All animals were ventilated at an inspired oxygen fraction of 25%, adjusting the rate to maintain a carbon dioxide tension of 35 to 45 mm Hg. Rectal temperature was kept at 35.5°C to 36.5°C. On the basis of previous experience,^{13,14} normal saline ($4 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), dopamine ($5-10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and epinephrine ($0.05-0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) were administered to maintain cardiovascular stability in the SVP group. Inotropic support was managed identically in sham-operated controls to allow meaningful comparisons. Minimal adjustments were made so as to maintain the systolic blood pressure as close as possible to baseline. Fresh whole blood was infused to replace

blood losses and maintain hemoglobin levels close to baseline. An identical protocol was used in controls.

Physiologic measurements were obtained at baseline (at least 2 hours after induction of anesthesia) and after conversion to SVP (at 30 minutes, 120 minutes, and afterload augmentation for 15 minutes). These included hemodynamic parameters, blood sampling for gas analysis, and determination of hemoglobin and lactate. Cardiac output (excluding coronary flow) was determined by use of a perivascular electromagnetic flowmeter, and MBF by microspheres. At completion, piglets were humanely killed with potassium chloride and fentanyl. An autopsy demonstrated the adequacy of the septostomy and aortopulmonary shunt. The LV free wall was excised. The subendocardium and subepicardium were divided by dissecting the myocardium in two layers (2-3 mm each). Sham-operated controls received identical preparation but were kept in a biventricular state. Measurements were obtained at baseline and after the simulated septostomy (at 30 minutes, 120 minutes, and afterload augmentation for 15 minutes).

Regional blood flow determinations. Stable-isotope microspheres ($15 \pm 5 \mu\text{m}$) (BioPhysics Assay Laboratory, Inc., Worcester, Mass) were used as described previously.¹³⁻¹⁵ Microspheres labeled with gold, samarium, ytterbium, and lutetium were administered over 3 to 5 seconds in the left atrium, while reference samples were collected over 90 seconds from the femoral artery (2 mL/min). A total of 1×10^6 microspheres were injected in the biventricular state, whereas 2.5×10^6 microspheres were injected in SVP. Tissue samples were weighed fresh, dried, and sent for analysis to BioPhysics Assay Laboratory for processing.¹⁵ Regional MBF was expressed in milliliters per minute per 100 gm, and calculated by normalizing the concentration of microspheres in the tissue sample to the concentration in the reference sample.¹³⁻¹⁵

Physiologic measurements and calculations. Total cardiac output (excluding coronary blood flow) was determined by an electromagnetic perivascular flowmeter (Transonic Systems Inc, Ithaca, NY) placed on the ascending aorta. Pulmonary blood flow was determined by placing the flowmeter on the pulmonary artery distal to the aortopulmonary shunt, as described by others.^{10,11} In SVP, total systemic blood flow was calculated as follows: Total cardiac output (mL/min) – Pulmonary blood flow (mL/min). Additional parameters were calculated by the following equations:

Coronary perfusion pressure (CPP) (mm Hg) = Aortic diastolic pressure (mm Hg) – Right atrial pressure (mm Hg).

Coronary resistance (mm Hg · mL⁻¹ · min · 100 g) = (Aortic diastolic pressure [mm Hg] – Right atrial pressure [mm Hg]) ÷ (MBF [mL · min⁻¹ · 100 g⁻¹]).

Subendocardial/subepicardial flow ratio = Subendocardial flow (mL · min⁻¹ · 100 g⁻¹) ÷ Subepicardial flow (mL · min⁻¹ · 100 g⁻¹).

Arterial oxygen content (Cao₂) (mL O₂/mL) = (Hemoglobin × 1.36 × Arterial oxygen saturation) + (0.0031 arterial oxygen tension).

Myocardial oxygen delivery (mL O₂ × min⁻¹ × 100 g⁻¹) = MBF × Cao₂.

Myocardial oxygen demand was estimated by the rate-pressure product (RPP), as previously described by others.¹⁶ To compensate for the substantial increase in total LV output occurring after conversion to SVP, we expressed the RPP as a multiple of the LV output increase from baseline, as shown by the following equation:

Myocardial O₂ demand = RPP × (SVP LV flow ÷ Baseline LV flow).

Statistical Analysis

All data were expressed as means ± SEM. One-way analysis of variance was used to compare variables within groups, whereas between-group comparisons were made by 2-way analysis of variance with Tukey post-hoc correction. The *t* test was used for statistical comparisons between the two groups at selected data collection points.

Results

Physiologic parameters are summarized in Table 1. Dopamine administration did not differ between the SVP and control group (from 7.1 ± 0.8 to 7.8 ± 0.8 to 6.5 ± 0.8 to $6.5 \pm 0.8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in SVP animals at baseline, 30 minutes, 120 minutes, and afterload, respectively, versus 8.5 ± 0.7 to 8.5 ± 0.7 to 8.5 ± 0.7 to $8.5 \pm 0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in controls: *P* = .7), nor did epinephrine administration (from 0.07 ± 0.01 to 0.07 ± 0.01 to 0.06 ± 0.01 to $0.06 \pm 0.01 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in SVP animals at baseline, 30 minutes, 120 minutes, and afterload, respectively, versus 0.06 ± 0.008 to 0.06 ± 0.008 to $0.06 \pm 0.008 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in controls: *P* = .9). Heart rate, systolic arterial pressure, and mean arterial pressure were comparable in both groups (*P* = not significant [NS]). Diastolic arterial pressure and CPP declined (*P* < .04) in SVP. Afterload augmentation resulted in higher heart rate, systolic arterial pressure, mean arterial pressure, and diastolic arterial pressure in both groups (*P* < .05) (Table 1). Total LV output increased by nearly 100% (*P* < .05) after conversion to SVP, whereas the proportion of flow directed to the systemic circulation (systemic blood flow indexed to body weight, expressed as milliliters per minute per kilogram) trended lower, in both the SVP and control groups (*P* = NS) (Table 1). Afterload augmentation caused a significant increase in systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, and CPP in both groups (*P* < .05).

Changes in the laboratory parameters during the experiment are illustrated in Table 2. Creation of SVP resulted in lower arterial oxygen saturation and Cao₂ (*P* < .05) at 30 minutes, while at 120 minutes such decline was lessened by a trend for higher hemoglobin levels and higher arterial oxygen saturation. Afterload augmentation resulted in a greater pulmonary blood flow, as shown by the higher pulmonary/systemic flow ratio, arterial oxygen saturation, Cao₂, and lower carbon dioxide tension (*P* < .05). Increased lactate and metabolic acidosis were noted in SVP at 30 minutes (Table 2). Table 3 summarizes changes in MBF, oxygen delivery, and coronary resistance in the subendocardial and subepicardial layers. These data are further illustrated in Figures 1, E2, and E3. There was a significant increase in MBF to the subendocardial and subepicardial

TABLE 1. Physiologic data

Variable	Group	Baseline	30 min	120 min	Afterload
Temperature (°C)	SVP	36.1 ± 0.2	35.1 ± 0.2	36 ± 0.3	35.9 ± 0.3
	Control	35.4 ± 0.2	35.8 ± 0.2	35.8 ± 0.2	35.8 ± 0.2
HR (beats/min)	SVP	160 ± 15	181 ± 7	195 ± 5	199 ± 5†
	Control	161 ± 5	180 ± 6	177 ± 3	195 ± 6†
SAP (mm Hg)	SVP	113 ± 4	114 ± 5	119 ± 5	157 ± 8†§
	Control	112 ± 8	118 ± 9	115 ± 7	150 ± 16†§
DAP (mm Hg)*	SVP	67 ± 4	47 ± 3†	55 ± 6	79 ± 3§
	Control	72 ± 7	80 ± 7	78 ± 8	125 ± 6†§
MAP (mm Hg)	SVP	84 ± 4	69 ± 4	79 ± 6	108 ± 4§
	Control	89 ± 6	94 ± 7	92 ± 7	134 ± 6†§
LAP (mm Hg)*	SVP	3.8 ± 0.5	6.2 ± 0.8	9.6 ± 1.7†	8.1 ± 2†
	Control	2.9 ± 0.5	3.5 ± 0.4	3 ± 1.1	12.7 ± 4.7††§
Total LV outflow indexed (mL · kg ⁻¹ · min ⁻¹)*	SVP	129 ± 13	202 ± 19†	226 ± 15†	233 ± 12†
	Control	130 ± 14	122 ± 18	101 ± 10	88 ± 18
SBF indexed (mL · kg ⁻¹ · min ⁻¹)	SVP	129 ± 13	109 ± 17	94 ± 7	86 ± 5
	Control	130 ± 14	122 ± 18	101 ± 10	88 ± 18
Qp/Qs	SVP	NA	0.9 ± 0.1	1.4 ± 0.1	1.7 ± 0.1‡
	Control	NA	NA	NA	NA
CPP (mm Hg)*	SVP	63 ± 4	41 ± 4†	46 ± 5	71 ± 4§
	Control	68 ± 6	76 ± 7	74 ± 7	107 ± 5‡§

SVP, Single-ventricle physiology; HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; LAP, left atrial pressure; LV, left ventricular; SBF, systemic blood flow; Qp/Qs, pulmonary/systemic flow ratio; CPP, coronary perfusion pressure; NA, not applicable. Values are expressed as mean ± SEM. **P* < .05 between groups (2-way analysis of variance [ANOVA]). †*P* < .05 as compared with baseline (1-way ANOVA). ‡*P* < .05 as compared with 30 minutes (1-way ANOVA). §*P* < .05 as compared with 120 minutes (1-way ANOVA).

muscle at 30 minutes in the SVP group (*P* < .05), whereas the subendocardial/subepicardial flow ratio and oxygen delivery were unchanged throughout the study in both groups (*P* = NS). Coronary resistance fell at 30 minutes in the SVP group (*P* < .05). During afterload augmentation, coronary

resistance was unchanged in both groups, although a trend for an increase was noted in controls (*P* = NS).

Myocardial oxygen supply/demand ratio declined at 120 minutes in SVP (*P* < .001), whereas it was unchanged in controls (Figure 2). During afterload augmentation, myo-

TABLE 2. Laboratory data

Variable	Group	Baseline	30 min	120 min	Afterload
Arterial pH	SVP	7.40 ± 0.03	7.25 ± 0.02†	7.28 ± 0.04	7.31 ± 0.04
	Control	7.39 ± 0.02	7.30 ± 0.02	7.33 ± 0.01	7.37 ± 0.02
Pco ₂ (mm Hg)	SVP	38 ± 3	47 ± 3	47 ± 3	33 ± 3‡§
	Control	33 ± 3	44 ± 3	39 ± 3	40 ± 2
Sao ₂ (%)*	SVP	98 ± 2	67 ± 2†	74 ± 2†	88 ± 1§
	Control	99 ± 1.4	98 ± 1.5	98 ± 1.5	98 ± 1
Hemoglobin (g/dL)	SVP	9.3 ± 0.5	9.4 ± 0.4	10.3 ± 0.3	10.1 ± 0.2
	Control	7.1 ± 0.4	8.6 ± 0.5	8.3 ± 0.4	9.1 ± 0.4
CaO ₂ (mL O ₂ /100 mL)	SVP	12.8 ± 0.7	8.5 ± 0.5†	11 ± 0.5	12.4 ± 0.3‡
	Control	10 ± 0.5	12 ± 1	11.8 ± 1.1	12.3 ± 1.2
Arterial lactate (mmol/L)	SVP	2.8 ± 0.4	11 ± 1.4†	8.9 ± 1.5†	10.3 ± 1.3†
	Control	3.9 ± 1.5	6.6 ± 1.5	6.4 ± 1.6	4.4 ± 1.2

SVP, Single-ventricle physiology; Pco₂, carbon dioxide tension; Sao₂, arterial oxygen saturation; CaO₂, arterial oxygen content. Values are expressed as mean ± SEM. **P* < .05 between groups (2-way analysis of variance [ANOVA]). †*P* < .05 as compared with baseline (1-way ANOVA). ‡*P* < .05 as compared with 30 minutes (1-way ANOVA). §*P* < .05 as compared with 120 minutes (1-way ANOVA).

TABLE 3. Changes in regional myocardial blood flow, subendocardial/subepicardial flow ratio, myocardial oxygen delivery, and coronary resistance over time

Variable	Group	Baseline	30 min	120 min	Afterload
Subendocardial flow ($\text{mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$)	SVP	247 $\pm$ 47	459 $\pm$ 101	311 $\pm$ 67	407 $\pm$ 74
	Control	243 $\pm$ 28	234 $\pm$ 30	208 $\pm$ 21	259 $\pm$ 73
Subepicardial flow ($\text{mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$)	SVP	213 $\pm$ 48	419 $\pm$ 88	312 $\pm$ 53	385 $\pm$ 70
	Control	181 $\pm$ 24	198 $\pm$ 33	180 $\pm$ 24	273 $\pm$ 57
Subendocardial/epicardial flow ratio	SVP	1.29 $\pm$ 0.1	1.1 $\pm$ 0.09	0.97 $\pm$ 0.08	1.04 $\pm$ 0.01
	Control	1.37 $\pm$ 0.08	1.26 $\pm$ 0.13	1.19 $\pm$ 0.08	0.94 $\pm$ 0.09
Subendocardial oxygen delivery ($\text{mL O}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$)	SVP	30 $\pm$ 5	41 $\pm$ 10	33 $\pm$ 6	51 $\pm$ 7§
	Control	24 $\pm$ 3	26 $\pm$ 2	22 $\pm$ 1.3	31 $\pm$ 10
Subepicardial oxygen delivery ($\text{mL O}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$)	SVP	26 $\pm$ 6	37 $\pm$ 9	33 $\pm$ 6	48 $\pm$ 9
	Control	17 $\pm$ 2	21 $\pm$ 2	20 $\pm$ 1.7	32 $\pm$ 7
Subepicardial resistance ($\text{mm Hg} \times \text{mL}^{-1} \times \text{min} \times 100 \text{ g}$)	SVP	0.34 $\pm$ 0.06	0.11 $\pm$ 0.05†	0.22 $\pm$ 0.07	0.23 $\pm$ 0.05
	Control	0.29 $\pm$ 0.04	0.40 $\pm$ 0.1	0.39 $\pm$ 0.08	0.56 $\pm$ 0.2
Subendocardial resistance ($\text{mm Hg} \times \text{mL}^{-1} \times \text{min} \times 100 \text{ g}$)	SVP	0.42 $\pm$ 0.09	0.12 $\pm$ 0.02†	0.22 $\pm$ 0.06	0.24 $\pm$ 0.05
	Control	0.42 $\pm$ 0.08	0.51 $\pm$ 0.14	0.46 $\pm$ 0.1	0.54 $\pm$ 0.23
Myocardial oxygen supply/demand (ratio)*	SVP	1.79 $\pm$ 0.1	1.14 $\pm$ 0.2†	0.68 $\pm$ 0.2†	0.83 $\pm$ 0.2†
	Control	1.42 $\pm$ 0.1	1.49 $\pm$ 0.1	1.48 $\pm$ 0.1	1.16 $\pm$ 0.2

SVP, Single-ventricle physiology. Values are expressed as mean $\pm$ SEM. * $P < .05$ between groups (2-way analysis of variance [ANOVA]). || $P < .05$ between the two groups at 30 minutes (t test). † $P < .05$ as compared with baseline (1-way ANOVA). § $P < .05$ as compared with 120 minutes (1-way ANOVA).

cardial oxygen supply/demand trended higher in SVP and lower in controls ($P = \text{NS}$).

Discussion

We previously demonstrated that acute SVP restricts oxygen availability to low-priority abdominal organs¹³ and partly to the brain.¹⁴ The focus of this investigation was to

study transmural MBF distribution in an acute model of SVP with aortopulmonary shunt and balanced pulmonary/systemic circulations and to investigate the effects of afterload augmentation. Our findings show that (1) SVP results in a significant decline in CPP such that MBF is maintained by a significant reduction in coronary resistance; (2) SVP does not alter the normal pattern of transmural flow distri-

Figure 1. Changes in coronary resistance ($\text{mm Hg} \cdot \text{mL}^{-1} \cdot \text{min} \cdot 100 \text{ g}$) during the experimental time points. Coronary resistance fell significantly after creation of SVP in both myocardial layers. Afterload augmentation caused a trend for higher coronary resistance in controls ($P = \text{NS}$), but not in SVP animals. * $P < .05$ within-group by 1-way analysis of variance (ANOVA).

Figure 2. Changes in myocardial oxygen supply/demand, estimated as myocardial oxygen delivery (microsphere method) divided by $RPP \times (SVP \text{ LV flow} \div \text{Baseline LV flow})$. Myocardial oxygen supply/demand fell after creation of SVP ($P < .03$, 1-way analysis of variance) and remained unchanged during afterload augmentation. The ratio did not change in controls throughout the experiment, although a downward trend was noted during afterload augmentation ($P = \text{NS}$). Differences between the two groups were statistically significant by 2-way analysis of variance ($P = .04$).

bution; (3) afterload augmentation in SVP does not result in malperfusion of the subendocardial muscle relative to the subepicardium; and (4) SVP causes a less favorable myocardial oxygen supply/demand relationship, whereas afterload augmentation does not worsen this balance.

Clinical studies on MBF in human SVP are scarce, and no experimental data are available. Donnelly and colleagues,⁹ using positron emission tomography, found lower resting MBF and coronary reserve in infants who received stage I Norwood palliation with a modified Blalock-Taussig shunt than in biventricular physiology. Fogel and coworkers³ studied myocardial perfusion in patients with hypoplastic left heart syndrome and found that MBF was greater in patients with univentricular physiology and a systemic-pulmonary shunt than in those after stage II palliation (hemi-Fontan procedure). They interpreted this phenomenon as the result of volume loading of the ventricle and greater myocardial energy requirements.

The consequences of diastolic hypotension, hypoxemia, and afterload augmentation on MBF have been investigated previously in dual-chambered physiology. Coronary flow, especially to the subendocardium, is determined by diastolic aortic pressure and duration of diastole.^{5,8,16-18} Severe diastolic hypotension can result in abnormal transmural flow distribution (malperfusion of the subendocardium relative to the subepicardium).^{8,17,18} During hypotension, the unequal distribution of MBF to the ventricular myocardium persists with tachycardia.⁸ Similar patterns of abnormal coronary flow distribution and relative subendocardial malperfusion can be provoked by severe afterload augmentation.¹⁷

We hypothesized that SVP with aortopulmonary connection could produce similar changes on MBF as a result of the diastolic runoff and that these could worsen with afterload increases. Our SVP model resulted in hypoxemia, diastolic hypotension, lower CPP, and higher volume load

on the ventricle. However, in contrast to previous studies,^{8,17} creation of SVP did not alter the normal transmural MBF distribution (subendocardial/subepicardial flow ratio; Figure E2). We hypothesize that the physiologic changes produced by the creation of our SVP model were insufficient to cause relative subendocardial malperfusion, as systemic and pulmonary circulations were balanced. This might not have been the case in the presence of a larger aortopulmonary shunt and more severe diastolic hypotension. The relative tachycardia observed in our piglets, partly the result of inotropic drugs, was unlikely a factor in our experiments. Buckberg and coworkers⁸ found that relative subendocardial malperfusion caused by arteriovenous fistulas was a rate-independent phenomenon.

Our study showed that SVP caused a significant decline in coronary resistance to sustain coronary perfusion, especially notable at 30 minutes (Figure 1). The creation of our model depended on the use of inotropic support to maintain hemodynamic stability. Therefore, we did not use coronary vasodilators to study coronary flow reserve, as these could have resulted in hemodynamic collapse. However, the observation of low coronary resistance to maintain adequate MBF in the face of low CPP suggests that the coronary circulation has a reduced capacity to vasodilate in response to increased myocardial oxygen demand. These findings would corroborate others' clinical observations of diminished coronary reserve⁹ and limited tolerance to hypotension⁴ in children with SVP and would support the use of techniques that avoid diastolic runoff and low CPP (ventricle-pulmonary connection).⁴

In our SVP model, we used the RPP to estimate myocardial oxygen demand, as described by others.¹⁶ Whereas this index correlates with wall stress, the primary determinant of myocardial oxygen demand,¹⁹ it does not take into account the significantly larger volume load on the ventricle

after conversion to univentricular physiology. Although stroke volume is not a primary determinant of myocardial oxygen demand, the magnitude of its increase was considerable and might have contributed to increasing oxygen demands. Therefore, we modified this index by including in the equation the increase in LV flow in SVP as compared with baseline (myocardial oxygen demand = $RPP \times [SVP \text{ LV flow} \div \text{Baseline LV flow}]$) to reflect this physiologic change, although we acknowledge that this method has limitations.¹⁹ Our findings of less favorable myocardial supply/demand relationship in SVP (Figure 2), compounded by the diminished coronary reserve, would explain the vulnerability to myocardial ischemia observed in human SVP.^{3,4,6}

Contrary to our hypothesis, afterload augmentation did not affect transmural MBF distribution, nor did it worsen myocardial oxygen supply/demand. Recent reports suggested that sudden increases in SVR in children with hypoplastic left heart syndrome could produce hemodynamic deterioration, increased pulmonary blood flow, reduced myocardial perfusion, and increased myocardial work.⁷ Our observations show that, in our SVP model, afterload augmentation restored CPP to normal levels, increased pulmonary blood flow through the shunt (increased pulmonary/systemic flow ratio, Table 1), and improved CaO_2 , leaving myocardial oxygen supply/demand unaffected. One possible explanation of the unchanged subendocardial/subepicardial flow ratio is that higher CPP promoted coronary flow during afterload augmentation (Table 1), while the negative effect of the increase in wall tension might have been lessened by greater runoff through the aortopulmonary shunt. In fact, during afterload increase, the left atrial pressure rose significantly in controls but not in SVP piglets (Table 1).

Limitations

Whether our findings translate to human SVP is unknown. Although this model attempts to reproduce human SVP, it is not identical to human SVP. These differences could influence coronary flow (ie, diminutive ascending aorta in neonates with hypoplastic left heart syndrome, right vs LV dominance, etc). This was an acute model, piglets were born with biventricular physiology, and the SVP pumping chamber was the LV. The need for sustained inotropic support and relatively low hemoglobin levels could have influenced our observations. An additional weakness relates to the central location of the aortopulmonary shunt, as a more peripheral insertion could have influenced our findings.²⁰ Also, we used aortic balloon inflation to manipulate afterload as this method is reproducible and has been validated previously.¹⁷ However, it might have produced changes that are not equivalent to clinical situations. Further, as small piglets tend to have reduced tolerance to cardiac manipula-

tions, we did not study coronary sinus blood for the potential concerns of altering MBF. We acknowledge that coronary sinus sampling could have provided useful information on the adequacy of MBF.

In conclusion, our study suggests that, in acute SVP, myocardial perfusion is maintained by lower coronary resistance. If these changes are sustained, the ability of the coronary system to further vasodilate in response to various stimuli may be reduced. Under our experimental conditions, the diastolic runoff of SVP did not alter the physiologic transmural distribution of MBF, although myocardial oxygen supply/demand balance was less favorable than in dual-chambered physiology. Our study also suggests that moderate afterload augmentation as observed in our physiologic model does not directly impair MBF nor does it alter transmural flow distribution, although these findings should be interpreted cautiously and in light of the many differences that our model has as compared with human SVP. Despite these limitations, our findings may expand the understanding of the mechanisms leading to myocardial ischemia in human SVP.

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Figure E1. Epicardial echocardiography showing the atrial septostomy and the absence of right ventricular distention.

Figure E2. Changes in MBF ($\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$) to the subendocardial and subepicardial muscle. SVP resulted in higher MBF to both subendocardium and subepicardium as compared with control, while the subendocardial/subepicardial ratio was unaffected. Afterload augmentation had no notable effect on MBF or transmural distribution. *Subendocardial/subepicardial flow ratio. *subendo*, subendocardial; *subepi*, subepicardial; *endo*, endocardial; *epi*, epicardial.

Figure E3. Changes in oxygen delivery ($\text{mL O}_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$) to the subendocardial and subepicardial muscle at different experimental data points. There was a trend for higher myocardial oxygen delivery to both layers of the myocardium after creation of SVP as compared with dual-chambered physiology. *subendo*, subendocardial; *subepi*, subepicardial; *ANOVA*, analysis of variance.