Severe Right Ventricular Pressure Loading in Fetal Sheep Augments Global Myocardial Blood Flow to Submaximal Levels

Mark D. Reller, MD; Mark J. Morton, MD; George D. Giraud, MD; David E. Wu, MS; and Kent L. Thornburg, PhD

**Background.** It has previously been shown that the fetal right ventricle (RV) is sensitive to changes in arterial pressure and that its stroke volume is significantly reduced with acute increases in pulmonary arterial pressure. However, the myocardial blood flow (MBF) response to increases in pulmonary arterial pressure have not been investigated in the fetus.

**Methods and Results.** To assess whether the RV afterload sensitivity to arterial pressure is associated with limitation in MBF, seven fetal lambs were instrumented at 130 days of gestation with a pulmonary arterial occluder and intravascular catheters. RV stroke volume was measured by an electromagnetic flow probe and MBF by 15-μm labeled microspheres. MBF was determined at baseline and during incremental increases in pulmonary arterial pressure. Maximal MBF was determined in seven additional fetuses during adenosine infusion. The highest tolerated pressure was associated with a 50% reduction in RV stroke volume. The highest pulmonary arterial occlusion pressure resulted in a doubling of MBF to all regions of the heart (266±99 to 504±158, 193±69 to 387±100, and 171±66 to 338±134 ml/min/100 g for the RV, septum, and left ventricle, respectively). The best correlation for increases in both RV and global MBF was the RV heart rate–systolic pulmonary pressure product. Adenosine infusion was associated with a threefold increase in global MBF that was significantly greater than the MBF achieved during pulmonary arterial occlusion.

**Conclusions.** The fetal RV sensitivity to acute pressure loading is not associated with limitation of MBF. The fetal myocardium has a remarkable flow reserve that allows for preservation of function during acute increases in arterial pressure. (*Circulation* 1992;86:581–588)

**KEY WORDS** • coronary circulation, fetal • adenosine • rate–pressure product • microspheres, radiolabeled

In the fetal circulation, the right and left ventricles pump “in parallel” and have similar filling and systolic arterial pressures. Despite similar hemodynamic environments, the two ventricles differ greatly in their morphology and function. Numerous studies have documented that the fetal lamb right ventricle ejects a larger stroke volume than the left ventricle and contributes a larger proportion of the combined fetal ventricular output. In addition, the two fetal ventricles differ in their afterload sensitivity to changes in arterial pressure. Although the ventricular wall thicknesses are comparable, the fetal right ventricular volume is not only larger than the left but has a circumferential radius of curvature to wall thickness ratio that is nearly twice as great. As this ratio is an important determinant of wall stress, and hence, myocardial oxygen consumption, it is reasonable to speculate that differences in wall stress may be an important determinant of coronary blood flow distribution in the fetus.

Although limited fetal data are available, numerous studies in the adult indicate that myocardial blood flow is tightly linked to metabolic need. Alterations that increase myocardial oxygen consumption (i.e., increased heart rate, contractility, wall stress) result in metabolically mediated coronary vasodilation. Although direct measurements of right ventricular myocardial oxygen consumption in the fetus are lacking, Fisher and colleagues have demonstrated that resting myocardial blood flow to the right ventricle exceeds that of the left ventricle, as predicted by their differential wall stresses.

It has previously been demonstrated that the fetus compensates for its relatively hypoxic environment (relative to the adult) by achieving greater resting myocardial flow. In addition, the fetus can further compensate during acute reductions in oxygen (up to 50% reduction in oxygen content) by increases in myocardial blood flow. However, the upper limit of coronary flow in the fetus is unknown. Because of its greater resting myocardial flow, it is possible that the fetal right ventricle may have a reduced coronary vasodilator reserve. If so, the fetal right ventricle could be particularly vulnerable to ischemia during periods of increased...
myocardial work (i.e., fetal arterial hypertension, partial ductus constriction).

The purpose of the present study was to measure the fetal myocardial flow response to acute and isolated increases in right ventricular pressure and to determine the maximum coronary vasodilator flow reserve. Our purpose was to test the hypothesis that the greater afterload sensitivity of the right ventricle is due to inadequate myocardial blood flow response (i.e., relative ischemia caused by demand–supply mismatch).

Methods

Animals

Ewes of mixed breeds were bred at our institutional farm to provide dated pregnancy and were brought to the laboratory pens several days before surgery to become accustomed to the surroundings. Fetuses of 130 days’ gestation were selected for instrumentation. Guidelines established by the Department of Animal Care at Oregon Health Sciences University were followed for the care and use of sheep.

Surgical Procedures

Ewes and fetuses underwent sterile surgery with protocols previously described.3–7 Anesthesia was induced with intravenous diazepam and ketamine and maintained with 1% halothane in nitrous oxide and oxygen. The fetus was delivered through a midline laparotomy and hysterotomy. Polyvinyl catheters (V-5, 1.3-mm o.d. or V-8, 1.7-mm o.d., Bolab Inc., Lake Havasu City, Ariz.) were placed in the right carotid artery and advanced to the brachiocephalic artery and in the right jugular vein and advanced to the right atrium (Figure 1).

A left thoracotomy was performed in the third intercostal space to gain access to the fetal heart. The pericardium was opened along the pulmonary artery from the pulmonary annulus on the right to the phrenic nerve to the left. The main pulmonary artery was dissected free. A V-5 catheter was placed just distal to the pulmonary annulus and secured with a purse-string suture. A snug-fitting electromagnetic flow sensor (C & C Instruments, Culver City, Calif.; In Vivo Metric, Healdsburg, Calif.) and an occluder (In Vivo Metric) were placed more distally on the main pulmonary artery proximal to the bifurcation (Figure 1). A V-5 catheter with a 4-mm V-8 tip was placed in the left atrium, and a 3-cm silicone rubber catheter with side holes was spliced to a long polyvinyl catheter and placed in the pericardial sac for measurement of pericardial pressure. The pericardial incision was left open for drainage during the postoperative period; the pericardium later seals during the postoperative recovery period. The thoracotomy was closed in layers. The fetus was returned to the uterus, and the uterus was closed. All catheters, the flow sensor, and the vascular occluder were tunneled to the side of the ewe, where they were kept in a nylon pouch. Penicillin (1 million units) was introduced into the amniotic cavity at the end of the procedure. After surgery, the ewes were brought to a clean pen, where they recovered from surgery for a minimum of 4 days before experiments were performed.

A second group of fetuses (n = 7) were similarly instrumented but without placement of the electromagnetic flow sensor or the occluder. A second V-5 left atrial catheter was placed for infusion of adenosine. In addition, a Doppler ultrasound probe was placed around the proximal circumflex coronary artery in four of the fetuses (Figure 1).

Laboratory Procedures

On the day of the experiment, the ewe was brought into the laboratory and placed in a stanchion. Fetal hydrostatic pressures were converted to electrical signals by ID Statham Gould pressure transducers (Gould Inc., Oxnard, Calif.). The pressures and flow signal were recorded on an eight-channel Gould RS 2000 polygraph recorder. Transducers were calibrated using a mercury manometer. All vascular pressures were referenced to the pericardial pressure. The flow sensors were calibrated in vitro using saline according to the manufacturer’s instructions. The flowmeter (Gould SP 2202) was adjusted to zero during diastole when pulmonary arterial flow was assumed to be zero.

Doppler-derived flow velocities were obtained using a directional pulsed Doppler flowmeter, model 545C-4 (University of Iowa, Iowa City). The Doppler flow signal was calibrated to a known voltage in which a
0.5-V deflection corresponded to 1-kHz Doppler frequency shift. Outputs from all channels were recorded onto floppy disks with a Hewlett-Packard 3437A system voltmeter and a 9826s computer (Desk Top Computer Division, Fort Collins, Colo.). Digital signals were sampled every 10 msec and averaged every 5 seconds. All output data from the disk were checked against the original strip chart records.

**Experimental Protocol**

With initial opening of the vascular catheters, arterial blood gas tensions, pH, and oxygen contents were measured. Only animals with an arterial Po$_2$ >18 mm Hg and pH >7.35 were accepted into the study.

**Protocol A: Effect of Acute Right Ventricular Pressure Loads**

Control values of vascular pressures, right ventricular output, and heart rate were recorded. The right ventricular stroke volume–pulmonary arterial pressure relation for each fetus was established by incremental occlusion of the pulmonary artery. Although we have previously demonstrated that the fetal right ventricle can tolerate acute increases in mean arterial pressure of approximately 20–25 mm Hg,35–7 the purpose of the initial stroke volume–pressure curve was to establish the highest pulmonary arterial pressure that was tolerated for each fetus. In previous studies, we found that fetal right ventricular stroke volume decreases in a near-linear fashion as pulmonary arterial pressure is increased up to a pressure beyond which stroke volume drops precipitously. This point was found to be reproducible in any given fetus. In the current study, we defined this "toleration point" as the highest pressure (during a stepwise arterial pressure increase) before the dramatic drop in stroke volume (Figure 2). Subsequently, the fetuses were allowed to recover for at least 30 minutes. After recovery, baseline regional and subregional myocardial blood flow measurements were made using 15-μm radiolabeled microspheres and the reference sample technique.14 Next, pulmonary arterial pressure was again increased by pulmonary arterial occlusion in three 5–8-mm Hg mean arterial pressure increments so that the last increment was at or near the toleration point of the stroke volume pulmonary arterial relation. Changes in right ventricular stroke volume during pulmonary arterial occlusion were measured by electromagnetic flow sensor similar to previous studies from our laboratory.3–7 After a minimum of 10 minutes at each pressure increment, myocardial blood flow measurements were again made using the reference sample technique.

**Protocol B: Determination of Coronary Blood Flow Reserve**

Maximal myocardial blood flow measurements were made in a separate group of seven fetuses during a continuous adenosine infusion into the left atrium. In the four fetuses instrumented with a Doppler ultrasonic probe placed on the proximal left circumflex coronary artery, an adenosine dose–flow response curve was constructed (Figure 3).

To assess the distribution of the left circumflex coronary arterial flow, methylene blue was injected into the vessel at the level of the ultrasonic probe in one of the fetuses. The flow distribution was primarily to the left ventricular free wall and a small portion of the anterior interventricular septum. Last, one of the seven protocol B fetuses was instrumented with a pulmonary arterial catheter, an electromagnetic flow sensor, a Doppler ultrasonic coronary probe, and an occluder so that the adenosine flow reserve could be measured during acute loading conditions in the same fetus. Changes in coronary flow velocities were assessed using the Doppler probe.

For myocardial blood flow determinations, 15-μm-diameter microspheres labeled with $^{105}$Ce, $^{85}$Sr, $^{51}$Cr, and
$^{68}$Nb were used. For each measurement, microspheres suspended in 10% dextran were injected into the left atrium over 30 seconds. The reference sample was withdrawn from the brachiocphalic artery at a withdrawal rate of 2.5 ml/min for 2 minutes.

After the ewes were killed, the fetal heart was removed, the great vessels were excised just above the valve leaflets, and the pulmonary veins and venae cavae were cut close to the atria. The right and left atria were dissected from the ventricles and from each other by dividing the atrial septum. Cross-sectional cuts through the ventricles were made, and the free walls of the right and left ventricles were separated from the septum. The ventricular free walls were dissected into inner (subendocardial) and outer (subepicardial) layers. All specimens were weighed and placed into vials, and radioactivity was determined using a Micrad germanium lithium gamma counter, model AMS-1(G) (Knoxville, Tenn.).

### Statistical Analysis

Hemodynamic values, arterial blood gas tensions and oxygen contents, right ventricular outputs, and regional myocardial blood flows were analyzed using ANOVA. When indicated by ANOVA, Tukey’s multiple comparison test was used to test for significant differences between conditions.

### Results

The studies in protocol A were performed in seven fetuses at a mean gestational age of 135.6±1.5 days (mean±SD) at 5.4 days after the operation (range, 4–7 days). The mean weight of the fetuses was 4.8±0.6 kg. The initial arterial blood gas measurements were normal in all fetuses (pH, 7.36±0.02; Pco$_2$, 48.9±3.0 mm Hg; po$_2$, 19.6±1.9 mm Hg; Cao$_2$, 8.3±1.4 ml/dl; hematocrit, 37.5±6.2%). Baseline hemodynamic measurements were found to be normal and similar to previous data from our laboratory.$^3$–$^5$ (Table 1, column 1).

For the purpose of comparison, the resting right ventricular stroke volume (1.26 ml/kg) was defined as 100%, and subsequent reductions during pulmonary arterial occlusion are listed as fractions of 100%. For the group, the mean right ventricular stroke volume-pulmonary arterial pressure relation is shown in Figure 4 and is similar to previous data published from our laboratory.$^3$–$^5$ As in these earlier studies, data points beyond the toleration point were not included. The mean slope was $-2.3\%$ stroke volume/mm Hg mean pulmonary arterial pressure.

The data obtained during pulmonary occlusion are shown in Table 1. Increase in the mean pulmonary arterial pressure from 52.8 to 70.5 mm Hg was associated with a nearly 50% reduction in right ventricular stroke volume. Pulmonary arterial occlusion was not associated with significant changes in either ascending aortic pressure or right atrial pressure. The highest tolerated occlusion pressure was associated with a significant increase in heart rate. Estimates of right and left ventricular work were made separately using the

### Table 1. Comparison of Hemodynamic Variables at Baseline and During Incremental Pulmonary Arterial Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PAP (mm Hg)</td>
<td>52.8±4.4</td>
<td>57.0±6.1</td>
<td>63.4±7.2</td>
<td>70.5±6.6*</td>
<td></td>
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<tr>
<td>Systolic PAP (mm Hg)</td>
<td>75.3±8.5</td>
<td>84.2±12.8</td>
<td>92.1±13.3</td>
<td>99.9±9.7*</td>
<td></td>
</tr>
<tr>
<td>RVS V (1.26 ml/kg=100%)</td>
<td>100%</td>
<td>93.1±7.6%</td>
<td>72.6±12.8%</td>
<td>52.1±18.4*</td>
<td></td>
</tr>
<tr>
<td>Mean CAP (mm Hg)</td>
<td>45.7±2.7</td>
<td>46.0±1.5</td>
<td>48.7±1.4</td>
<td>45.6±2.8</td>
<td></td>
</tr>
<tr>
<td>Systolic CAP (mm Hg)</td>
<td>57.9±6.0</td>
<td>56.5±6.0</td>
<td>60.6±4.2</td>
<td>58.3±6.7</td>
<td></td>
</tr>
<tr>
<td>Diastolic CAP (mm Hg)</td>
<td>38.2±4.3</td>
<td>39.2±3.6</td>
<td>41.1±2.4</td>
<td>38.7±3.1</td>
<td></td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>4.1±1.5</td>
<td>3.4±1.8</td>
<td>4.9±2.0</td>
<td>4.9±1.6</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>141±21</td>
<td>147±23</td>
<td>155±18</td>
<td>182±29*</td>
<td></td>
</tr>
<tr>
<td>RV (R×P)</td>
<td>10,744±2,606</td>
<td>12,537±3,614</td>
<td>14,455±3,657</td>
<td>18,101±2,872*</td>
<td></td>
</tr>
<tr>
<td>LV (R×P)</td>
<td>8,219±1,821</td>
<td>8,280±1,545</td>
<td>9,407±1,333</td>
<td>10,703±2,619</td>
<td></td>
</tr>
</tbody>
</table>

PA, pulmonary arterial; PAP, PA pressure; RVS V, right ventricular stroke volume; CAP, carotid arterial pressure; RV and LV (R×P), right ventricular and left ventricular rate–pressure product.

* Different from columns 1 and 2; p<0.05.

† Different from columns 1, 2, and 3; p<0.05.

![Graph of mean percent reduction in right ventricular stroke volume vs. mean increment in pulmonary arterial pressure from baseline for the seven fetuses in protocol A. Slope for the regression line is $-2.3\%$ stroke volume/mm Hg pulmonary arterial pressure. Regression data do not include points obtained during precipitous drop in right ventricular stroke volume.](Image)
double product (systolic arterial pressure times heart rate). The left ventricular double product did not change significantly during progressive pulmonary occlusion.

The regional myocardial blood flow at baseline and in response to pulmonary arterial occlusion are shown in Table 2. Resting myocardial flows to the right ventricular free wall, the interventricular septum, and the left ventricular free wall, 266±99, 193±69, and 171±66 ml/min/100 g tissue, respectively, are comparable to previous data published by Fisher and colleagues.11-13 The myocardial flows at the highest pulmonary pressure for the right ventricular free wall, interventricular septum, and left ventricular free wall were increased by 90%, 101%, and 98%, respectively (Table 2). The correlation that best predicted the progressive increase in both the right ventricular and the global myocardial blood flow was the right ventricular double product calculation (Figure 5).

The subendocardial portions of the right and left ventricular free walls were found to have relatively greater flow than the subepicardial portion. The flow to both the subendocardial and subepicardial portions increased during pulmonary occlusion, and no significant changes in the flow ratio occurred even at the highest pulmonary arterial pressure measured (Table 2).

In the seven fetuses in which the adenosine dose–flow response was determined (protocol B), maximal coronary flow velocities were obtained at left atrial adeno-
sine infusion rates greater than 60 μg/kg/min. The mean maximal adenosine dosage infused for the seven fetuses was 63 μg/kg/min. Increases in left circumflex coronary Doppler flow velocities were found to correlate with left ventricular free wall flow by use of radiolabeled microspheres (r=0.81, p=0.011).

Baseline arterial blood gas tensions were pH, 7.38±0.02; Pco₂, 43.1±3.8 mm Hg; Po₂, 19.7±2.2 mm Hg; CaO₂, 7.9±1.2 ml/dl; and hematocrit, 34.9±5.1%. These data were comparable to the protocol A fetuses. Adenosine infusion was not associated with significant changes in systemic arterial pressure, right atrial pressure, or mean heart rate (Table 3). The maximal myocardial blood flow during adenosine infusion was 757±269, 614±178, and 602±192 ml/min/100 g for the right ventricular free wall, the interventricular septum, and the left ventricular free wall, respectively. These flows are significantly greater than the maximal flows seen at the highest pulmonary arterial pressure in protocol A (p<0.05).

To assess the myocardial vasodilator reserve during maximal pulmonary artery occlusion in the same fetus, one fetus had a modification of both protocols performed. Subsequent to the initial assessment of myocardial flow at baseline and during adenosine infusion (protocol B), changes in coronary flow velocities during pulmonary arterial occlusion with and without adenosine were obtained using the Doppler coronary probe. When compared with the coronary flow velocities obtained at maximal pulmonary occlusion, the coronary flow velocities increased an additional 55% when adenosine was infused to reach flow velocities identical to those seen when adenosine was infused alone.

**Discussion**

Although limited data currently exist concerning the coronary circulation in the fetus, it is recognized that the fetus compensates for its relative hypoxemic environment by maintaining a greater resting myocardial blood flow so that oxygen delivery and myocardial oxygen consumption are comparable to those seen in the adult.12 It is also known that the fetus can compensate during acute reductions in oxygen by further augmenting myocardial blood flow,13 although the upper limits of this flow have not been investigated. It is recognized that acute hypoxemia in the fetus may be associated with the development of arterial hypertension15-17; however, the selective effect of increased
arterial pressure (and hence, myocardial work) on right ventricular myocardial blood flow is unknown.

Earlier studies have shown that increased arterial pressure has a negative effect on fetal ventricular stroke volume.3-5,18,19 Our own work has shown that the fetal right ventricle has a greater sensitivity to changes in arterial pressure than does the left ventricle.3,5 Because of its greater resting wall tension and myocardial blood flow,11-13 we hypothesized that the fetal right ventricle may be vulnerable to ischemia during periods of increased myocardial work. If so, potential limitation of myocardial blood flow might account for its greater afterload sensitivity to increased arterial pressure.

The ability of the fetal right ventricle to maintain normal function during increases in arterial pressure above baseline should be partly determined by the extent to which coronary flow can increase. Although no fetal data have previously existed, it is known that acute increases in right ventricular pressure in the adult circulation are associated with a significant coronary vasodilatory response.20-24 However, when maximal coronary vasodilatation is reached, further pressure increases result in right ventricular failure as a consequence of ischemia and the resultant discrepancy between oxygen and substrate supply and demand.21-24

In the present study, increases in arterial pressure resulted in decreases in right ventricular stroke volume (Figure 4) predicted by earlier studies.3,5,6 The mean pulmonary arterial pressure—right ventricular stroke volume relation was stable for pressure increases in the physiological range (up to 25 mm Hg). Myocardial blood flow changes were assessed during incremental pressure increases up to an assessment just below the maximally tolerated pressure. Acute increases in right ventricular pressure were associated with a progressive increase in myocardial flow, ultimately reaching a level that was about twice that of the resting myocardial blood flow (Table 2). Importantly, the increase in right ventricular myocardial flow was not associated with any significant change in the subendocardial—subepicardial flow ratio. These data indicate that a significant myocardial flow reserve was present and was achieved without evidence of subendocardial ischemia.

Increasing arterial pressure load (myocardial work) to the right ventricle should be associated with an increase in right ventricular myocardial oxygen consumption. However, in an in vivo fetal preparation, indexes of myocardial work (i.e., wall tension and contractility) are difficult to estimate. Another difficulty is the inability to collect right ventricular venous outflow because the bulk of coronary flow to the right ventricle drains directly into the right heart via thebesian veins,25 preventing the measurement of right ventricular oxygen or substrate extraction.

The product of heart rate and peak systolic pressure, the so-called rate—pressure product, has been shown to correlate with measured left ventricular myocardial oxygen consumption26,27 and has been used by previous investigators studying the fetal circulation.10-12 However, its applicability as an estimate of right ventricular work and myocardial oxygen demand in the fetus is unknown. Thus, it is of interest that the best predictor of right ventricular myocardial blood flow response was the calculated heart rate—pulmonary arterial pressure product (Figure 5). Although these data are potentially useful as an indicator of right ventricular myocardial demand, limitations of the double product preclude any conclusions that changes in myocardial flow reflect commensurate changes in myocardial oxygen consumption.

An important question unanswered by the data in this study relates to the cause of the precipitous drop in right ventricular stroke volume. The evidence against this being due to the onset of myocardial ischemia is indirect. First, based on the progressive increase in myocardial flow found in this study, there was no evidence of "plateauing" of the flow response. Furthermore, although there was a tendency for a decrease in the ratio of subendocardial—subepicardial flow with increasing arterial pressure, the decrease was not significant. In addition, there was no evidence for any significant increase in right atrial pressure, a finding that argues against the development of right ventricular dysfunction and is expected near the onset of myocardial ischemia.21-24 Last, the adenosine data indicate a significant flow reserve significantly greater than the flow achieved.

### Table 3. Hemodynamics and Regional Myocardial Blood Flow at Baseline and During Adenosine Infusion

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Adenosine infusion (63 μg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean CAP (mm Hg)</td>
<td>47.4±5.3</td>
<td>46.5±4.9</td>
</tr>
<tr>
<td>Systolic CAP (mm Hg)</td>
<td>59.6±4.6</td>
<td>60.2±3.7</td>
</tr>
<tr>
<td>Diastolic CAP (mm Hg)</td>
<td>38.6±2.7</td>
<td>38.4±3.5</td>
</tr>
<tr>
<td>Right atrial pressure' (mm Hg)</td>
<td>3.7±1.3</td>
<td>4.2±0.9</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>165±20</td>
<td>167±22</td>
</tr>
<tr>
<td>Myocardial blood flow (ml/min/100 g)</td>
<td>200±51</td>
<td>620±181*</td>
</tr>
<tr>
<td>Right ventricular flow (ml/min/100 g)</td>
<td>253±55</td>
<td>757±269*</td>
</tr>
<tr>
<td>Right ventricular inner/outer</td>
<td>1.10±0.06</td>
<td>0.97±0.12</td>
</tr>
<tr>
<td>Septal flow (ml/min/100 g)</td>
<td>224±61</td>
<td>614±178*</td>
</tr>
<tr>
<td>Left ventricular flow (ml/min/100 g)</td>
<td>197±62</td>
<td>602±192*</td>
</tr>
<tr>
<td>Left ventricular inner/outer</td>
<td>1.07±0.13</td>
<td>1.00±0.13</td>
</tr>
</tbody>
</table>

CAP, carotid arterial pressure.
*Significantly different from baseline and from maximal flow achieved during pulmonary occlusion (column 4, Table 2); p<0.05.
'Not measured in three of the fetuses.
during pulmonary occlusion. Although only one fetus had an assessment of myocardial blood flow during pulmonary occlusion with and without adenosine, changes in the coronary flow velocity suggest that a significant coronary flow reserve was still present at the maximally tolerated pulmonary pressure.

Because coronary flow varies with and is dependent on coronary perfusion pressure, it is important to note that the coronary arterial pressure and right atrial pressure were similar during adenosine infusion and during pulmonary occlusion. Thus, it is likely that the coronary perfusion pressure was similar during the two sets of observations. The extent to which acute increases in right ventricular pressure above systemic levels could additionally alter coronary perfusion to the right ventricular myocardium remains incompletely answered from the data in this study.

The adenosine data obtained in this study are the first to determine the maximal coronary flow reserve in the fetus. Maximal coronary vasodilator reserve has been used in the postnatal circulation to give useful information as to the potential response during maximal stress.28 The data from these experiments demonstrate that a maximal myocardial blood flow response was achieved when >60 μg/kg/min was infused into the left atrium. The Doppler-derived coronary flow velocities were found to correlate significantly with the coronary flow measurements obtained using the microsphere technique. These flows indicated that the maximum myocardial flow reserve exceeded baseline myocardial flow by about threefold. In addition, right ventricular myocardial blood flow exceeded the left by approximately 30% at baseline and during adenosine infusion. Thus, the myocardial blood flow reserve for the two fetal ventricles appears to be similar.

The current study demonstrates that acute increases in right ventricular pressure were associated with a doubling of myocardial blood flow from baseline values; the unexpected finding was that the myocardial blood flow response was global and included the left ventricle and the interventricular septum. Thus, while the left ventricular heart rate–ascending aortic pressure product was unchanged during pulmonary occlusion, nearly identical increases in left ventricular myocardial flow also occurred. This finding suggests that either a vasodilator substance was released in response to acute right ventricular pressure or that left ventricular wall stress increases may have occurred secondary to ventricular interaction that were not reflected by changes in the left ventricular rate–pressure product. Alternatively, although the left ventricular double product did not reach statistical significance, a significant increase in heart rate did occur. Thus, it is possible that a larger sample size might have detected an increased double product that, if present, would indicate that an increase in left ventricular myocardial oxygen consumption explains the increase in left ventricular myocardial blood flow. Further study, including measurement of oxygen and metabolic substrate consumption, is necessary to resolve this issue.

Summary

There is no evidence that limitation of myocardial blood flow contributes to the enhanced afterload sensitivity of the fetal right ventricle to changes in arterial pressure up to the point of acute right ventricular failure. The data from the current investigation demonstrate that the fetal right ventricle has a significant capacity to increase coronary flow in response to acute increases in pulmonary arterial pressure. Importantly, the response to acute right ventricular pressure load was found to be global with significant right and left ventricular myocardial hyperemia. We conclude that the fetal myocardium has a remarkable reserve that allows preservation of function during acute reductions in oxygen content and during increases in arterial pressure.

References


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*Circulation.* 1992;86:581-588
doi: 10.1161/01.CIR.86.2.581
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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