Effects of Increasing Afterload on Left Ventricular Output in Fetal Lambs

John Hawkins, George F. Van Hare, Klaus G. Schmidt, and Abraham M. Rudolph

Fetal ventricular performance has been considered limited because ventricular output does not increase with rapid volume expansion above mean left atrial pressures (mLAPs) of 5–7 mm Hg. To explore relations between preload, afterload, and stroke volume (SV) in the fetal left ventricle, we instrumented 126–129 days gestation fetal lambs with ascending aortic electromagnetic flow transducers, vascular catheters, and inflatable occluders around the aortic isthmus (n=8) or descending aorta (n=7). At 24–48 hours after surgery, blood was withdrawn or infused to reach various mLAPs. The aorta was then slowly occluded as aortic flow and mean arterial pressure (MAP) were measured continuously. Isthmus constriction produced linear decreases in SV as MAP increased; mLAP was unchanged. Descending aortic constriction produced no decrease in SV until high MAPs were reached. SV decreased as MAP increased further, and mLAP rose significantly. The curve relating mLAP and SV before constriction showed little increase in SV above mLAPs of 5–7 mm Hg; however, when curves were derived relating SV and mLAP at relatively constant MAPs, SV continued to increase even above an mLAP of 8–10 mm Hg. Our studies indicate that the fetal left ventricle responds to progressive increases in mLAP to at least 10 mm Hg. The lack of increase in SV above an mLAP of 5–7 mm Hg with rapid volume expansion is related to the concomitant increase in MAP and afterload. (Circulation Research 1989;65:127–134)

Previous studies by several investigators have examined the effects of both preload (filling pressures) and afterload (arterial pressures) on fetal ventricular function. The Frank-Starling mechanism has been shown to operate over the range of normal filling pressures in the fetal heart.1–3 At resting filling pressures, fetal ventricular output and stroke volume are near maximum and can be increased only slightly by volume infusion. The relation between fetal ventricular function and afterload has also been investigated in early studies by Rudolph and Heymann4 and in more recent reports by both Gilbert5 and Thornburg and Morton.6,7 In the fetal lamb, although changes in arterial pressure markedly decrease right ventricular stroke volume, they have been thought to have relatively little effect on left ventricular stroke volume.4–7

Materials and Methods

Animals

We studied 10 fetuses from pregnant ewes of mixed western breed. Breeding dates were known,
and gestational ages ranged from 126 to 129 days (0.85–0.90 gestation).

**Surgical Preparation**

Maternal ewes were fasted for 48 hours before the operation; they then were blindfolded and underwent epidural or spinal anesthesia with 1% tricaine. Polyvinyl catheters (0.127 cm i.d.) were inserted into a maternal pedal artery and vein; 0.9% saline was administered to the mother throughout the procedure as well as ketamine (100 mg) when necessary for sedation. The fetus was exposed through a midline maternal laparotomy and a hysterotomy. A fetal hind limb was then exposed, and after local anesthesia with 1% lidocaine subcutaneously, polyvinyl catheters (0.102 cm i.d.) were inserted into the pedal artery and vein and advanced into the descending aorta and inferior vena cava, respectively. The fetal chest was exposed and anesthetized with 1% lidocaine subcutaneously and deeply. Through a left thoracotomy performed in the fetal fourth intercostal space, a polyvinyl catheter (0.076 cm i.d.) was placed in the left internal mammary artery and advanced into the brachiocephalic trunk. The pericardium was then opened widely, avoiding injury to the phrenic nerve. A left atrial catheter (0.076 cm i.d.) was placed through a purse-string suture in the left atrial appendage. A previously calibrated electromagnetic flow transducer (C and C Instruments, Culver City, California) was placed around the aortic isthmus between the brachiocephalic trunk and the ductus arteriosus. In eight of these eight fetuses, a silicone rubber inflatable cuff (specially made in our laboratory) was then placed around the aortic isthmus between the brachiocephalic trunk and the ductus arteriosus. In four of these eight fetuses, a second balloon occluder was placed around the descending aorta distal to the ductus arteriosus. The remaining three fetuses had only descending aorta occluders placed. After these were secured, an 8F polyvinyl catheter was placed into the pleural space for drainage. The pericardium was left open to prevent any possible constriction of the heart or tamponade effect. The fetal ribs were then approximated, and the thoracotomy was closed in separate layers.

The fetal neck and head were then exposed through the same uterine incision used for the thoracotomy. To prevent fetal breathing movements, 5 mg succinylcholine was administered intravenously. After local anesthesia with 1% lidocaine, both carotid sheaths were exposed through a single neck incision. An 8F polyvinyl catheter was placed into a jugular vein and advanced into the superior vena cava for withdrawal and infusion of blood for the volume studies. A polyvinyl catheter (0.076 cm i.d.) was placed in one of the carotid arteries and advanced into the brachiocephalic trunk. Catheters specially made in our laboratory, consisting of 1 cm lengths of 12F polyvinyl tubing, were placed around both vagus nerve trunks. Each of these sheaths was supplied by a catheter (0.038 cm i.d.) for irrigation of the sheath and vagal trunks.

After catheter placement was completed, the neck incision was closed, and the catheters and flow transducer cable were tunneled out the left flank of the ewe and placed in a vinyl pouch. The ewe was then returned to her cage; she received daily intravenous and intra-amniotic doses of penicillin 6 potassium (500,000 units) and kanamycin (300 mg) until all studies had been completed.

**Afterload Studies**

After 24–48 hours recovery from surgery, the maternal ewe was placed in a study cart with food and water, where she remained for the duration of the fetal studies. Fluid-filled catheters were connected to Statham P23Db pressure transducers (Statham Instruments, Oxnard, California) calibrated to the nearest 1 mm Hg with a static mercury column. Continuous recordings of mean and phasic aortic, mean amniotic, and mean left atrial pressures were recorded on a Beckman (San Jose, California) eight-channel direct writing recorder. Heart rate was measured by a cardiotachometer triggered by the phasic aortic pressure signal. Phasic and mean ascending aortic blood flows were measured from the electromagnetic flow probe on a Statham SP2202 flowmeter and recorded continuously. Stroke volume (excluding coronary blood flow) was calculated by dividing ascending aortic blood flow by heart rate.

Before studies were begun, arterial blood gases were obtained from the carotid artery in each fetus. Only those fetuses with a pH >7.35, Po2>17 mm Hg, and O2 saturation >40% were studied. After control hemodynamic measurements were taken, vagal blockade was achieved by instilling about 0.25 ml of 2% lidocaine into each vagus nerve catheter. Lidocaine was rein infused approximately every 20 minutes (usually three times per study) to ensure continuous blockade of the baroreceptor response. A second set of hemodynamic measurements was taken before commencing the experimental studies.

To describe fetal ventricular function curves, left atrial pressures were adjusted by withdrawal of fetal blood or infusion of fresh heparinized whole blood obtained either from a twin fetus under sterile conditions or from the mother if fetal blood was unavailable. Function curves were obtained at four different mean left atrial pressures: 1) during resting conditions (control), 2) after withdrawal of approximately 50 ml fetal blood, 3) after infusion of 50 ml blood, and 4) after infusion of 100 ml blood.
Baseline hemodynamic measurements were made at each left atrial pressure after 5–10 minutes to allow the fetus to come to a steady state.

While hemodynamic measurements were recorded continuously, the isthmus or descending aortic balloon occluder was gradually inflated over 30–60 seconds and then was deflated. Typically, inflation of the isthmus balloon resulted in a 15–20 mm Hg increase in mean aortic pressure, and inflation of the descending aortic balloon, a 25–35 mm Hg increase. These increases in mean aortic pressure amounted to five to seven data points for the isthmus occlusion function curves and eight to 10 data points for the descending aorta occlusion function curves. Ten to 15 minutes were allowed between function curves or further inflation of an occlusion balloon for the pressures and flows to return to baseline or steady state. Arterial blood gases were monitored between each function curve; the experiment did not proceed if fetal pH dropped more than 0.04 units. After all function curves had been completed, the catheters were flushed, filled with heparin solution, and closed, and the ewe was returned to her cage.

**Pressure-Volume Studies**

Left ventricular pressure-volume studies were performed on the day after the afterload study in four animals. Left ventricular end-systolic and end-diastolic volumes were determined from cross-sectional echocardiographic imaging using an Advanced Technology Laboratories (Bothell, Washington) Mark 600 sector scanner with a 3.5 MHz mechanical transducer. Attempts were made to perform the echocardiographic study with the ewe standing in a cart, but adequate recordings could not be obtained through the maternal abdomen because of maternal movements, intestinal gas, and distance involved. Therefore, the ewe underwent a second epidural or spinal anesthesia and a second laparotomy, and cross-sectional echocardiography was performed on the exposed uterus. Fetal left atrial pressure was adjusted to the same levels used in the afterload study by infusion or withdrawal of blood. At each level of left atrial pressure, equivalents of apical four-chamber and apical two-chamber views were obtained. In addition, the left atrium was mapped for mitral regurgitation using pulsed Doppler ultrasound examination incorporated into the same instrument used for imaging.

All studies were recorded on 0.5-inch videotape for later replay and analysis. Using a Microsonics 886 system (Indianapolis, Indiana) end-diastolic and end-systolic frames were digitized and stored for volume calculation. The frame at mitral valve closure or before aortic valve opening was defined as the end-diastolic frame, and the frame just before mitral valve opening or at aortic valve closure was defined as the end-systolic frame. The endocardial surface was outlined, and left ventricular end-diastolic and end-systolic volumes were calculated using a biplane Simpson's algorithm as previously described.8-10 Five cardiac cycles were averaged for each measurement.

After the study was completed, the ewe and fetus were killed using intravenous pentobarbital; the fetus was autopsied to obtain the exact weight and to confirm positions of the catheters, occlusion balloons, and flow probe.

**Statistical Analysis**

Function curves were plotted for each animal relating stroke volume per kilogram of body weight to mean aortic pressure at each of the four left atrial pressures studied. Results for studies with descending aortic occlusion were simply plotted for each resting left atrial pressure. Results for studies with aortic isthmus occlusion were fitted to straight line regression equations at each left atrial pressure. From each animal's regression line, the slope was determined, as well as the mean arterial pressure corresponding to a stroke volume of 0.75 ml/kg. These values at each mean left atrial pressure were compared using Friedman's test.11 When Friedman's test was statistically significant, multiple comparisons were carried out using the Wilcoxon signed-rank test and the Bonferroni correction.12 Other continuous variables were analyzed by analysis of variance (ANOVA).11 In all analyses, differences were considered statistically significant if p<0.05.

**Results**

Ages at the time of study ranged from 126 to 129 days (127±1, mean±SD) and weights ranged from 1.6 to 3.9 kg (2.9±0.6). Resting descending aortic blood gases before the study showed pH of 7.37±0.05, P O2 20±4.2 mm Hg, P CO2 of 55±7.9 mm Hg, and O2 saturation of 50±11%. Blood gases did not change appreciably during the studies except for the O2 saturation, which tended to decrease slightly when maternal blood was used for transfusion. Resting heart rate averaged 171±15.5 beats/min, resting mean aortic pressure 44.7±3.9 mm Hg, stroke volume 0.80±0.1 ml/kg, and mean left atrial pressure 3.19±0.80 mm Hg. These values were similar to resting hemodynamic values observed in animals of similar age in our laboratory.13 Vagal blockade with lidocaine did not alter resting heart rate, aortic blood flow, or aortic blood pressure. In addition, heart rate was not changed at the various left atrial pressures following vagal blockade or with complete occlusion of either the aortic isthmus or the descending aorta (p>0.25 for all, ANOVA).

Figure 1 shows the effects of aortic isthmus occlusion on left ventricular stroke volume and aortic pressure in eight fetuses. Aortic pressure increased 15–20 mm Hg, an increase adequate to significantly change stroke volume and generate function curves. Whereas the function curve relating stroke volume to aortic pressure at the lowest left atrial pressure was nearly flat, the function curves at higher left atrial pressures were steeper and had negative slopes (p<0.01, Friedman's test;
for A vs. B and A vs. C, \( p < 0.05 \) by Wilcoxon signed rank test with Bonferroni correction. The curves at higher left atrial pressures had similar slopes but were progressively shifted to the right as left atrial pressure increased \( (p < 0.05 \) for B vs. C and B vs. D, Friedman test, with Wilcoxon signed rank test and Bonferroni correction for multiple comparisons). Despite total aortic isthmus occlusion, the change in left atrial pressure from the resting values at each pressure level studied was not statistically significant (Table 1) \( (p < 0.05 \), ANOVA).

Figure 2 shows the effects of descending aortic occlusion on left ventricular stroke volume and aortic pressure. The function curves from these studies typically were relatively flat at lower aortic pressures, where stroke volume changed little, and steeper at higher aortic pressures, where stroke volume decreased dramatically with increasing arterial pressure. The four curves were all similar in shape but were shifted in position upward and to the right for progressively higher left atrial pressures (Figure 2). Resting left atrial pressures were similar to those in the isthmus occlusion experiments but increased as the descending aortic balloon was inflated (Table 1) \( (p < 0.05 \), ANOVA).

Figure 3 shows the effects of left atrial pressure on stroke volume. Because these experiments involved infusion of blood to change left atrial pressures, aortic pressure increased unavoidably. To analyze the independent effects of filling and arterial pressures on stroke volume, we selected data points from all experiments (isthmus and descending aorta occlusions) for left atrial pressures and stroke volumes that fell within a narrow range of arterial pressure. This allowed construction of function curves at a relatively constant aortic pressure. The first curve (A) represents the stroke volume obtained at the four resting left atrial pressures, without inflation of either occlusion balloon. It features a steep ascending limb and a nearly flat plateau limb above left atrial pressures of 5-6 mm Hg. The two other curves (Figures 3B and 3C) represent average stroke volumes and filling pressures obtained at aortic pressures 47.5-52.5 and 67.5-72.5 mm Hg. At a relatively constant aortic pressure, stroke volume continued to increase as left atrial pressures increased, even above the 5-6 mm Hg level. At higher aortic pressures (67.5-72.5

### Table 1. Left Atrial Pressures at Rest and During Aortic Occlusion

<table>
<thead>
<tr>
<th>Isthmus occlusion (mm Hg)</th>
<th>Descending aorta occlusion (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td>Occlusion</td>
</tr>
<tr>
<td>0.9 ±0.6</td>
<td>1.1±0.7</td>
</tr>
<tr>
<td>3.5 ±0.9</td>
<td>3.7±1.1</td>
</tr>
<tr>
<td>6.7 ±1.2</td>
<td>7.3±1.6</td>
</tr>
<tr>
<td>10.2 ±1.2</td>
<td>10.8±1.2</td>
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<tr>
<td></td>
<td>0.5±0.6</td>
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<td>3.0±1.6</td>
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<td>6.0±1.7</td>
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<td>10.5±0.9</td>
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\*\( p < 0.05 \), ANOVA.
mm Hg) the curve remains similarly shaped but is shifted to the right and downward from the curve at lower pressure (47.5–52.5 mm Hg).

Four of the fetal lambs underwent acute pressure-volume studies using echocardiography to determine left ventricular end-diastolic volumes and to look for mitral regurgitation. Figure 4 shows the effect of left atrial filling pressures on left ventricular end-diastolic volume. At left atrial pressures above 2 mm Hg, diastolic volume increases linearly. This relation appears to be linear even up to left atrial mean pressures of 10–11 mm Hg. Even at the highest left atrial pressures, pulsed Doppler examination showed no mitral regurgitation in any of the animals.

Discussion

Our results demonstrate the effects of arterial pressure on fetal left ventricular stroke volume under two different loading conditions: with left atrial pressure constant and with left atrial pressure increasing. We have shown, as did Thornburg and Morton,7 that the fetus is able to maintain left ventricular stroke volume in the face of increased arterial pressure (Figure 2) but only with compensatory rises in left atrial pressure. However, we have shown that aortic pressure has a strongly negative effect on fetal left ventricular stroke volume when filling pressures remain constant (Figure 1). Along with others,6–7 we have demonstrated that the fetal left ventricle has a limited ability to increase stroke volume above left atrial filling pressures of 5–7 mm Hg with volume infusion. However, when aortic pressure is held relatively constant, left ventricular stroke volume continues to rise, even above left atrial filling pressures of 10 mm Hg (Figure 3). Our preparation allows a relatively independent examination of the effects of increasing left atrial pressures and aortic pressures on left ventricular stroke volume and function.

To properly study fetal ventricular function, studies must be designed so there is no interference with either the adrenergic state of the fetal animal or the contractile state of the myocardium. In previous studies of the effect of arterial pressure on fetal stroke volume, arterial pressure has been altered with methoxamine,3 phenylephrine, and nitroprusside.6,7 Both phenylephrine14 and methoxamine14,15 have been shown to have some positive inotropic effect in both sheep and man. We therefore chose to alter aortic pressure by constricting the aorta using surgically placed occluders. We chose not to use nitroprusside to examine stroke volume at lower
arterial pressures because of the unavoidable changes in left atrial pressure that this would cause. Our method, however, allowed examination of a sufficient range of aortic pressures for meaningful function curves to be generated (Figures 1 and 2). Constriction of the aorta may have increased catecholamine concentrations in the fetus because of the decrease in aortic pressure that inevitably occurred distally in the aorta and adrenal glands. However, we felt that blockade of any catecholamine effect with \( \alpha \)- or \( \beta \)-blockers would result in marked changes in the shape of function curves,\(^{16}\) making data even more difficult to interpret.

Our preparation is unique in that it allows observation of the effects of increasing afterload on stroke volume while preload remains constant in the resting, in utero fetus. Preparations in which preload is allowed to increase in response to increasing afterload are complicated by the effect of "preload reserve"; that is, the increase in left atrial pressure compensates for the increasing afterload's negative effect on stroke volume via the Frank-Starling mechanism.\(^{17}\)

Our experiments were also designed to minimize the vagally mediated bradycardia and baroreceptor response to increased aortic pressure without systemic pharmacological interventions. Previous studies have achieved this either by using hexamethonium to achieve ganglionic blockade\(^5\) or by blocking muscarinic and \( \beta \)-adrenergic receptors using a combination of atropine and propranolol.\(^6,7\) At the doses of propranolol used in Thornburg and Morton's studies (1 mg/kg), \( \beta \)-adrenoreceptor blockade is nearly complete, yet resting hemodynamic values were minimally changed.\(^6,7\) Klopfenstein and Rudolph\(^{16}\) have shown in newborn lambs that although this dose of propranolol does not significantly alter resting aortic flow or filling pressures, the response to volume infusion is markedly blunted and altered as compared with those animals not receiving propranolol. Thus, eliminating the use of \( \beta \)-adrenergic receptor blockade would seem important in studies specifically examining ventricular function under varying left atrial pressures.

In our first attempts to achieve baroreceptor blockade without the use of pharmacological intervention, we used the denervation technique of Itskovitz and Rudolph.\(^{18}\) However, the extensive surgery was associated with a high fetal mortality. We then used a simple method involving localized instillation of lidocaine around the vagus nerves to block the vagally mediated bradycardic response to increased aortic pressure. This method was not associated with significant fetal mortality, did not alter resting hemodynamic values, and effectively blocked the bradycardic response to increased aortic pressure.

Our study of the effect of increasing arterial pressure on left ventricular stroke volume used occluders on the fetal aorta at two different sites to produce two conditions of left atrial pressure change: 1) left atrial pressure remained constant with aortic isthmus occlusion (Figure 1), and 2) left atrial pressure increased with descending aortic occlusion distal to the ductus arteriosus (Figure 2). The mechanism for the two different left atrial pressure responses involves changing patterns of shunting across the foramen ovale. When the aortic isthmus occluder is inflated, left ventricular stroke volume decreases immediately, resulting in increased end-systolic volume in the left, but not the right, ventricle. During the subsequent diastolic filling, some of the blood that would normally cross the foramen ovale to enter the left atrium is presumably diverted to the right ventricle, resulting in an unchanged mean left atrial pressure. On the other hand, descending aortic occlusion increases the afterload to both ventricles, which in turn increases end-systolic volume in both ventricles but without any mechanism for diversion of venous return. Consequently, there is a progressive increase in both right and left atrial pressures (Table 1). Thus, left atrial pressure rises with descending aortic occlusion, the same response obtained in studies by Thornburg and Morton\(^6,7\) as well as Gilbert\(^2\) using phenylephrine.

In our study, when left atrial pressures were held constant, there was a linear, inverse relation between arterial pressure and stroke volume. At the three higher left atrial pressures examined, this relation differed only in the position of the response curves relative to one another (Figure 1). This linear relation has not previously been described in the fetal heart but is similar to that seen in the adult dog and cat under acute conditions when preload is held constant by complex instrumentation.\(^{17,19,21}\)

At the lowest left atrial pressure (2 mm Hg), the relation between arterial pressure and stroke volume was still linear but nearly flat, implying that aortic pressure has little effect on stroke volume when left atrial pressures are low (Figure 1). This observation is unexplained. Although we found a linear relation between left atrial pressure and end-diastolic volume, during isthmus balloon constriction in our preparation, the end-diastolic volume possibly was rising despite the lack of significant change in mean left atrial pressure. Such an increase in end-diastolic volume might increase stroke volume by the Frank-Starling mechanism as it did in our animals with descending aortic constriction.

The pericardium was left open to avoid possible pericardial tamponade. It is possible that the lack of the normal pericardial diastolic effect (increased ventricular stiffness) might have changed the ventricular pressure-volume relation. However, these pericardial effects are normally only important at high filling pressures\(^{22}\) and cannot explain our finding of significantly different curves at the lowest filling pressures. The pericardium has been shown to play an important role in mechanical interaction between the right and left ventricles. Volume loading of one ventricle acts to shift the pressure-volume relation of the opposite ventricle upwards. This effect is
dramatically reduced by removal of the pericardium. Because isthmus occlusion in our preparation likely causes right ventricular volume loading by diversion of blood from the left ventricle, it was important to leave the pericardium open to minimize such ventricular interactions.

A second possible explanation involves the concept of arterial compliance, which contributes to the afterload on the ventricle. In the hypovolemic state, the arterial system is less distended and, therefore, more compliant than in the normovolemic or hypervolemic state. Increases in arterial resistance (by balloon constriction) may not affect the afterload to the left ventricle as much because of the highly compliant arterial system, which keeps afterload low. In volume-loaded states, the arterial system is less compliant and would be less able to compensate for increases in resistance induced by inflation of the isthmus balloon.

Although the initial portions of our curves with descending aortic constriction and rising left atrial pressure are similar to responses observed by Thornburg and Morton, at higher aortic pressures, stroke volume is markedly reduced (Figure 2). This may be explained by the exhaustion of "preload reserve." Preload reserve, the compensatory increase in stroke volume resulting from the increased ventricular filling and diastolic volume that accompany increases in afterload, allows ventricular output and stroke volume to be maintained during periods of increased afterload. Once the preload reserve is exhausted at the higher aortic pressures, stroke volume is rapidly reduced by higher afterloads or aortic pressure.

Similarly, the later portions of our function curves indicate that at high aortic pressures, the preload reserve of the fetus becomes exhausted and aortic pressure markedly reduces stroke volume (Figure 3). We do not know why this phenomenon was not seen in Thornburg and Morton’s studies. The phenylephrine used in their studies may have had a positive inotropic effect and allowed stroke volume to be maintained even at the highest aortic pressures.

Although both our study and that of Thornburg and Morton used mean arterial pressure as an index of afterload, some have advocated vascular impedance as a potentially better index. Impedance represents the pulsatile nature of the circulation and all the factors that contribute to the arterial load, such as arterial distensibility, blood viscosity, and cross-sectional area of the vascular bed. Impedance more completely characterizes the ventricle’s dynamic load than does arterial pressure. Calvin and associates have shown that pulmonary artery constriction produces a greater increase in impedance than does microvascular injury. Pulmonary artery constriction both reduces arterial distensibility and increases the total resistance, while vascular injury only increases resistance without changing vascular distensibility. In Thornburg and Morton’s study, afterload may have been increased to a lesser degree than in our study due to the different methods used. Phenylephrine and nitroprusside would be expected to affect only the peripheral resistance, while aortic constriction would be expected to increase resistance and decrease distensibility.

The shape of the fetal cardiac function curve relating left ventricular stroke volume to left atrial pressure has been well documented in past studies that have used volume infusion techniques and is nearly identical to the curve generated in our study (Figure 3, curve A). The curve is characterized by a steep ascending limb between left atrial pressures of 0-4 mm Hg and a plateau limb above 5-7 mm Hg where increases in left atrial pressure produce little further increase in stroke volume. Because normal fetal resting mean left atrial pressures are in the range of 5-7 mm Hg, it has been thought that the fetal left ventricle normally functions at the top of the cardiac function curve and that its ability to increase output by raising venous return is therefore limited.

Previous volume infusion experiments have, however, failed to take adequate account of the increases in arterial pressure, and therefore afterload, that occur with volume loading. We feel that such increases in afterload decrease stroke volume and thus are responsible for the plateau limb of the fetal cardiac function curve. By studying a preparation in which arterial pressure and left atrial pressure were both controlled, we were able to construct fetal cardiac function curves at constant arterial pressures (Figure 3, curves B and C). In these curves, stroke volume continued to increase above the left atrial pressures of 5-7 mm Hg, exhibiting no plateau. If arterial pressure does not increase, then the fetal heart seems to have the ability to increase its left ventricular output by augmenting venous return.

McPherson et al have suggested that the plateau in the previous volume-infusion fetal function curves may be explained by the lower compliance of fetal myocardium compared with newborn or adult myocardium. They suggest that left ventricular volume changes very little above left atrial pressures of 5-7 mm Hg. However, both in our studies and in those of Romero et al and Kirkpatrick et al, left ventricular end-diastolic volume continues to increase almost linearly to filling pressures of 10-12 mm Hg. Increased fetal cardiac compliance, then, seems an unlikely explanation for the plateau in the fetal cardiac function curve at left atrial pressures of 5-7 mm Hg. It may be important, however, at left atrial pressures above 10-12 mm Hg.

In summary, we have demonstrated that preload plays an important role in left ventricular response to changes in arterial pressure in fetal lambs. The Frank-Starling mechanism is operational in the fetus and allows the fetal heart to adapt to increased arterial pressure by maintaining left ventricular stroke volume. However, the mechanism by which the fetus increases left ventricular stroke volume and output at birth remains unexplained. Increases
in aortic pressure at birth would be expected to decrease ventricular output, the opposite of what actually occurs. Changes in preload are small at birth and in themselves cannot explain the twofold increase in left ventricular output that occurs in the perinatal period. Contractility is known to increase after birth\(^{29,30}\); increased contractility as well as hormonal changes\(^ {31}\) may play a large role in the increase in cardiac output that occurs after birth. Further examination of this question will require studies of changes in fetal myocardial contractility and their effect on the ventricular response to increased afterload.

References


Key Words: cardiac performance, ventricular function, volume loading, preload, cardiac output, stroke volume
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