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Determinants of Increased Left Ventricular Output during *In Utero* Ventilation in Fetal Sheep

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ABSTRACT

A model of *in utero* ventilation was used to elucidate the mechanisms by which left ventricular (LV) output increases with the transition from a fetal to a neonatal circulation. Using a conductance catheter, LV volumes were measured in seven anesthetized, near-term fetal sheep. Pressure-volume data was recorded before and with oxygen ventilation and again after occlusion of the umbilical cord. Ventilation caused increases in LV end-diastolic volume (2.3 ± 0.9 to 2.9 ± 0.6 mL/kg; $p < 0.05$), stroke volume (1.2 ± 0.3 to 1.9 ± 0.2 mL/kg; $p < 0.001$), and ejection fraction (52.8 ± 11.1 to 66.4 ± 8.8%; $p < 0.001$). Contractile state, as assessed by end-systolic elastance, did not change during the transition. Heart rate also remained constant. Afterload, as assessed by effective arterial elastance, decreased from 1.80 ± 0.37 to 1.04 ± 0.33 kPa/mL ($p < 0.01$). Occlusion of the umbilical cord did not result in any further change in hemodynamic parameters. Pressure-volume analysis revealed that a decrease in effective LV afterload and an increased LV end-diastolic volume are the major determinants of, and contribute comparably to, the profound increase in LV output with *in utero* ventilation. Enhanced contractility is not required for the increase in LV output to occur. (***Pediatr Res* 36: 373–379, 1994**)

Abbreviations

LV, left ventricle
RV, right ventricle
dP/dt_{max}, the maximum of the first time derivative of the LV pressure wave form
E_{es}, end-systolic elastance
E_{aLV}, effective arterial elastance (afterload opposing LV ejection)
PV, pressure-volume

Adaptation of the fetus to extrauterine life involves a number of rapidly occurring processes. Among these, the initiation of breathing and the transition from a fetal to a neonatal circulation are the paramount events. In the fetal heart, which is characterized by RV dominance (1–3), the ventricles operate in parallel. After birth, the ventricles function serially and LV output increases 2- to 3-fold (4–10). The mechanism by which the LV increases its output to such an extent remains a mystery.

In utero ventilation is associated with a marked increase in LV output identical with the increase observed in the immediate postpartum state. Either an increase in end-diastolic volume, ejection fraction, or both may underlie the augmented LV stroke volume. Ejection fraction could increase due to an increase in contractility or a reduction in afterload. Augmented LV end-diastolic volume as a result of increased pulmonary venous return (11–15) and an increase in contractility (16, 17) have both been suggested to play a role in augmenting LV output at birth. Because systemic pressure is increased or unchanged at birth, it has been suggested that a decrease in afterload is unlikely to occur (18). On the other hand, afterload may decrease due to the exposure of the LV to the pulmonary circulation through the patent ductus arteriosus (19). The individual contribution of each component to the augmentation of LV performance at birth is unknown.

We applied the conductance catheter technique to the *in utero* ventilation model. This technique, which provides continuous and instantaneous measurements of ventricular volume, allowed changes in LV end-diastolic volume, stroke volume, and ejection fraction to be determined. Contractility was assessed by E_{es}, a relatively load- and heart rate–independent index (20, 21), and the E_{aLV} was used to evaluate afterload (22, 23). This study furthers our understanding of the mechanisms by which the LV increases its output during the transition from a fetal to a neonatal circulation.

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METHODS

Surgical procedure. This study was approved by the Mount Sinai Hospital Animal Care Committee following the guidelines of the Canadian Council for Animal Care. Surgery was performed on seven pregnant ewes between 138 and 141 d of gestation. Anesthesia was induced with i.v. thiopental sodium and maintained by positive pressure ventilation with 1–1.5% isoflurane and oxygen. A vascular catheter was placed in the femoral artery of the ewe to monitor maternal blood pressure and gases. The upper part of the fetus was then withdrawn through a uterine incision up to the insertion of the umbilical cord. A catheter was placed in an axillary artery to obtain fetal blood gases. An inflatable cuff occluder was then sewn around the umbilical cord. The occluder was constructed from the balloon of a Foley catheter (75-mL capacity) tethered inside a Fiberglas screen cuff. During experiments, the cuff was inflated with 60 mL of air to gently occlude the umbilical cord over a 6-cm length. The function of the occluder was confirmed at necropsy. A 2 F catheter-tip pressure transducer (Millar, Houston, TX) was introduced through a left carotid artery cutdown, advanced into the LV, and positioned such that no impact artifact was evident. A custom-made, 4 F, eight-electrode conductance catheter was similarly advanced through the same carotid artery and positioned in the LV such that its distal electrode was at the apex and the most proximal electrode cephalad of the aortic valve. Correct placement of the conductance catheter in the LV was determined by monitoring the segmental volume phase relationships and counterclockwise PV loop formation. The conductance catheter total electrode spacing was 4 cm, the appropriate length being established from LV long axis measurements previously made on fetuses of the same gestational age. Correct catheter position was confirmed at necropsy. A venous line was advanced through the left jugular vein to the right atrium. A tracheostomy tube (5-mm inner diameter) was placed in the trachea through a midline neck incision, and a T-connector (4-mm inner diameter) was used to attach it to the inflow and outflow tubes (5-mm inner diameter) with the junction made at the trachea to minimize dead space. The fetus was then replaced and the uterine incision closed.

Experimental protocol. Hemodynamic recordings were acquired during three phases of the experiment: *1*) during a control period, *2*) during ventilation with 100% oxygen and, *3*) during oxygen ventilation after umbilical cord occlusion. Before each set of hemodynamic recordings, fetal arterial blood samples (0.3 mL) were obtained and immediately analyzed for gas tensions and pH using a blood gas analyzer (model 170, Corning Medical, Medfield, MA) and temperature corrected to 39°C. At each phase, steady state, instantaneous LV PV data were digitally recorded with both maternal and fetal ventilators off at end-expiration.

The experimental protocol began with control fetal recordings taken after surgery, when hemodynamic parameters were observed to be stable. Tracheal fluid was then allowed to drain by gravity, and the inflow and outflow tubes were connected to a volume-regulated ventilator (model LS104–150, Bourns, Riverside, CA). To cause a maximal decrease in pulmonary vascular resistance, the fetuses were ventilated with 100% oxygen, with ventilator settings adjusted to deliver a tidal volume of about 10 mL/kg at a rate of 30–50 breaths/min with peak inspiratory pressures not exceeding 40 cm H_2O. A positive end-expiratory pressure of 5–8 cm H_2O was applied to offset amniotic pressure. Arterial blood gases and oxygen saturations were measured, and the ventilator settings were adjusted until acceptable values were reached (Hb O_2 saturation $\geq$ 90%, a decrease in $P_{CO_2} \geq$ 1.33 kPa). Ventilation was maintained for at least 15 min, after which hemodynamic recordings were taken. The umbilical cord occluder was then inflated, with PV data being acquired simultaneously. Hemodynamic recordings were taken again 20 min after cord occlusion.

Hemodynamic data acquisition and analysis. The principles, technique, and validation of the conductance catheter method of LV volume estimation are described in detail elsewhere (24–30). Briefly, the conductance catheter was connected to a Z-*cath* signal conditioner (IVM Systems Inc., Willowdale, Ontario, Canada) that applied an excitation current to the outer electrodes and measured the five segmental conductances (G_i) between intervening electrode pairs. The instantaneous LV volume was then obtained by:

$$V(t) = \frac{L^2 \cdot \rho}{\alpha}\left(\sum_{i=1}^{5} G_i(t) + \frac{1}{3}G_1(t)\right) - V_c$$

where α is a unitless, empirical coefficient relating conductance catheter–derived stroke volume to actual stroke volume; α was assumed to be 1 in this study. L is the interelectrode spacing, and ρ is the specific electrical resistance of blood that was measured with a 0.5-mL cuvette at each phase of the experiment. The parallel conductance volume, V_c, is a correction term required to account for the conductivity of structures surrounding the LV blood pool. It was determined by a dilution method (26), whereby the conductivity of blood was transiently altered by a bolus injection of 0.3 mL of 3 M NaCl into the right atrium. A portion of the saline immediately shunted through the foramen ovale and entered the LV, the remainder entering the RV. The saline entering the RV may have affected parallel conductance, thus rendering the first LV wash-in curve unreliable. Of the saline that entered the RV, a portion passed through the pulmonary circulation, which resulted in a second LV wash-in curve (Fig. 1). By the time the second curve was observed, most of the saline would have washed out of the RV. Thus, the second response was used to compute V_c and was the mean value obtained from three consecutive saline injections. Left ventricular pressure, five segmental conductances, and ECG were digitized (250

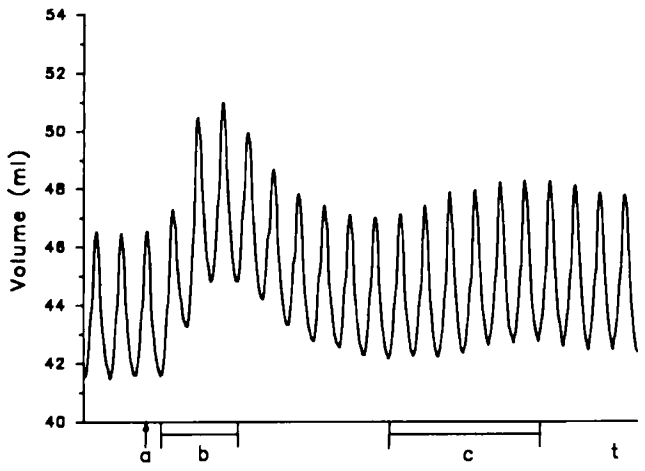

Figure 1. Example of the dual saline wash-in response of the fetal LV. Time of injection of hypertonic saline is indicated by the *arrow* (*a*). The first transient increase in the signal (*b*) is a result of saline shunted through the foramen ovale. The second transient increase (*c*), which is used for calculation of parallel conductance volume, is a result of saline washing into the LV after passing through the lungs.

Hz, 12 bit) on an IBM AT compatible computer and stored on hard disk for subsequent analysis.

Left ventricular stroke volume and heart rate were measured and LV output and dP/dt_{max} computed during each phase of the experiment. Contractility of the LV was assessed by E_{es}, which was computed by single-beat analysis of the PV loop under steady state conditions using the "cosine" method (24, 31):

$$E_{es} = \frac{\left(\frac{dP}{dt_{max}} \cdot \frac{T}{2\pi} + P_{DC}\right) - P_{es}}{V_{ed} - V_{es}}$$

where T is the period of an extrapolated isovolumic contraction and is estimated as twice the interval from time of dP/dt_{max} to dP/dt_{min}, P_{DC} is the pressure at which dP/dt_{max} occurs, V_{es} and P_{es} are the volume and pressure at end-systole, which was defined as the time when the maximum ratio of LV pressure to volume occurs, and V_{ed} was defined as the maximum volume. Afterload opposing left ventricular ejection was assessed by measuring E_{aLV}, the ratio of LV end-systolic pressure to stroke volume.

PV loop analysis was used to estimate the relative contributions of changes in end-diastolic volume (V_{ed}) and E_{aLV} to changes in stroke volume (SV) (Fig. 2). First, the SV after ventilation was predicted assuming an isolated increase in V_{ed} by:

$$SV = V_{ed} \cdot EF_{BL} \quad (1)$$

where EF_{BL} is the baseline ejection fraction. The impact of reduced E_{aLV} on SV was then determined by assuming no change in E_{es} or V_{ed}. E_{es} and E_{aLV} can be expressed as:

$$E_{es} = \frac{P_{es}}{V_{es} - V_0} \quad (2)$$

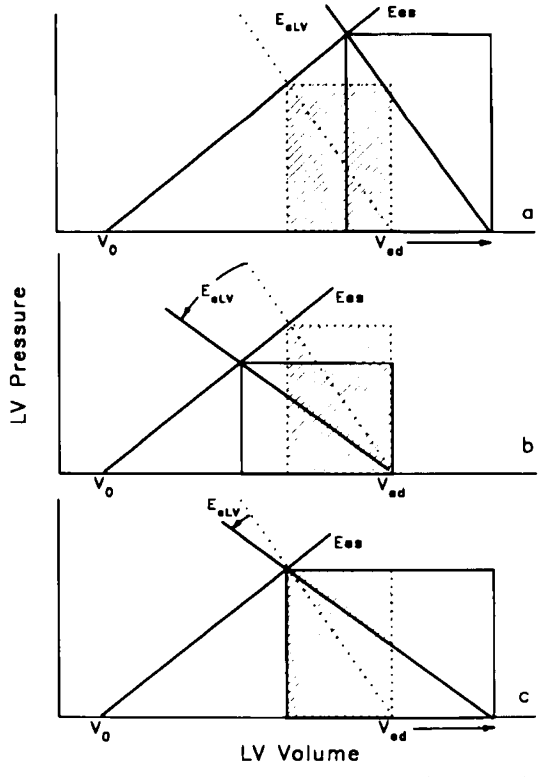

Figure 2. Schematic diagram using the PV plane to illustrate the effects of reduced effective LV afterload (E_{aLV}) and increased end-diastolic volume (V_{ed}) on LV stroke volume when contractility, measured by E_{es}, remains constant. The *hatched rectangles* represent control PV loops. An isolated increase in V_{ed}, with E_{aLV} unchanged, would result in an increased stroke volume, generating a higher systolic pressure (*a*). An isolated reduction in E_{aLV}, V_{ed} unchanged, would also result in an increased stroke volume at a lower systolic pressure (*b*). When decreased E_{aLV} is combined with an increased V_{ed}, the effects on stroke volume and systolic pressure are additive (*c*).

$$E_{aLV} = \frac{P_{es}}{V_{es} - V_{ed}} \quad (3)$$

where V_{es} and P_{es} are end-systolic volume and pressure and V_0 is the volume axis intercept of the E_{es} line. Equations 2 and 3 were then rearranged and equated to give an expression for V_{es}:

$$V_{es} = \frac{E_{es} \cdot V_0 - E_{aLV} \cdot V_{ed}}{E_{es} - E_{aLV}} \quad (4)$$

Substitution for V_0 from equation 2 allows prediction of SV by:

$$SV = V_{ed} - \frac{E_{es} \cdot V_{es} - E_{aLV} \cdot V_{ed} - P_{es}}{E_{es} - E_{aLV}} \quad (5)$$

The increases in SV predicted by equations 1 and 5 were then expressed as a percentage of the observed increase by:

$$\frac{SV_{predicted} - SV_{baseline}}{SV_{observed} - SV_{baseline}} \times 100 \quad (6)$$

Statistical analysis. All variables and derived parameters were calculated from an average of 20 consecutive

cardiac cycle measurements. A paired *t* test was used to compare control data with values obtained during ventilation and ventilation data with values obtained after cord occlusion. Significance was assumed at the $p < 0.05$ level. For control and ventilation periods, data are presented from seven animals. One animal was excluded from the cord occlusion stage due to technical difficulties. All data are expressed as mean ± 1 SD.

RESULTS

Fetal body weights were 4.63 ± 1.02 kg (range 2.88 to 5.90 kg). During the control period, arterial pH, Po_2, Pco_2, and O_2 saturation were within the normal range for fetuses at this stage of gestation (Table 1). As expected, arterial Po_2 and O_2 saturation increased with oxygen ventilation. There was a decrease in Pco_2 and an increase in pH due to mild hyperventilation of the fetuses. Occlusion of the umbilical cord did not cause any further alterations in fetal arterial blood gases or pH.

Hemodynamic measurements taken at each stage of the experiment are summarized in Table 2. Ventilation caused a significant increase in LV output, principally as a result of increased stroke volume; heart rate remained relatively stable. The effects of ventilation on fetal PV loops are presented in Figure 3. LV end-diastolic volume and ejection fraction increased with ventilation. Although systolic blood pressure remained unchanged, E_{aLV} decreased. *In utero* ventilation was not associated with a change in either dP/dt_{max} or E_{es}. Measurements taken while the umbilical cord was being occluded showed a transient increase in end-systolic pressure (17.7 ± 8.5%, $p < 0.001$) and a decrease in stroke volume (11.2 ± 6.3%, $p < 0.01$), reflecting an increase in E_{aLV} (33.5 ± 16.2%, $p < 0.01$) (Fig. 4). Twenty min after cord occlusion, however, all hemodynamic parameters returned to levels not significantly different from those obtained with ventilation alone (Table 2).

With ventilation alone, the increase in end-diastolic volume resulted in 58.4 ± 20.5% and the reduction in E_{aLV} caused 45.4 ± 4.0% of the observed increase in stroke volume. After cord occlusion, the relative contributions to the increase in stroke volume from baseline were 60.2 ± 3.7% and 46.6 ± 8.9%, respectively. The difference between these contributions did not reach statistical significance at either stage of the experiment.

Table 1. *Fetal arterial blood gases during experiments**

	Control	O_2 ventilation	Occlusion
pH	7.37 ± 0.03	7.46 ± 0.06†	7.45 ± 0.06
Po_2 (kPa)	3.29 ± 0.68	17.88 ± 12.18‡	17.17 ± 10.34
Pco_2 (kPa)	5.71 ± 0.81	4.21 ± 0.56†	3.85 ± 0.80
O_2 saturation (%)	46.2 ± 9.7	95.3 ± 5.8†	96.6 ± 3.5

* Data are presented as mean ± 1 SD. Occlusion data were obtained 20 min after umbilical cord occlusion.

† $p < 0.001$ *vs* the value during the immediately preceding stage.

‡ $p < 0.05$ *vs* the value during the immediately preceding stage.

Table 2. *Fetal hemodynamic measurements during experiments**

	Control	O_2 ventilation	Occlusion
Heart rate (beats/min)	153 ± 15	164 ± 20	158 ± 26
EDV (mL/kg)	2.3 ± 0.9	2.9 ± 0.6†	3.0 ± 0.7
Stroke volume (mL/kg)	1.2 ± 0.3	1.9 ± 0.2‡	1.7 ± 0.2
Ejection fraction (%)	52.8 ± 11.1	66.4 ± 8.9‡	61.2 ± 12.5
LV output (mL/kg/min)	179.7 ± 51.9	311.6 ± 59.6§	280.7 ± 77.3
E_{aLV} (kPa/mL)	1.80 ± 0.37	1.04 ± 0.33§	1.09 ± 0.47
E_{es} (kPa/mL)	1.57 ± 0.37	1.41 ± 0.47	1.49 ± 0.43
dP/dt_{max} (kPa/s)	201 ± 30	229 ± 53	237 ± 47
Systolic pressure (kPa)	9.41 ± 0.33	9.33 ± 0.75	9.36 ± 0.68

* Data are presented as mean± 1 SD. Occlusion data were obtained 20 min after umbilical cord occlusion. EDV, end-diastolic volume.

† $p < 0.05$ *vs* the value during the immediately preceding stage.

‡ $p < 0.001$ *vs* the value during the immediately preceding stage.

§ $p < 0.01$ *vs* the value during the immediately preceding stage.

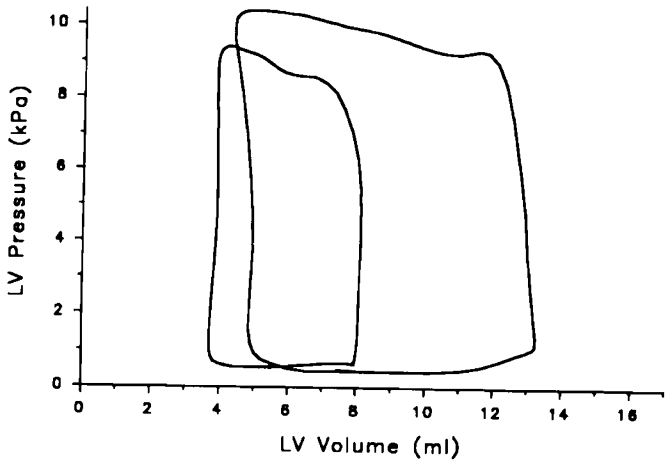

Figure 3. Left-ventricular PV loops recorded at control (*smaller loop*) and during oxygen ventilation.

DISCUSSION

Using the conductance catheter technique, absolute fetal LV volumes were measured during *in utero* ventilation. We found a marked increase in LV end-diastolic volume, stroke volume, and ejection fraction associated

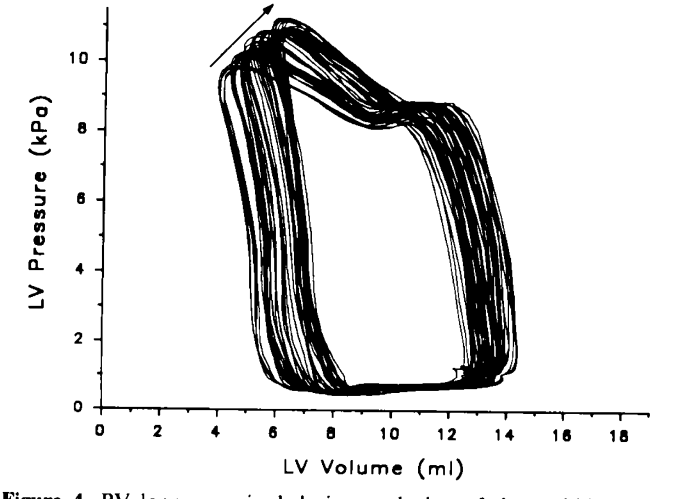

Figure 4. PV loops acquired during occlusion of the umbilical cord showing a definite increase in afterload. The *arrow* indicates the direction of change during umbilical occlusion.

with a reduction in effective LV afterload as measured by E_{aLV}. The increased end-diastolic volume further augmented stroke volume, allowing systolic blood pressure to be maintained after the transition. Contractility, as assessed by E_{es}, was found to play no role in the increased LV output observed with *in utero* ventilation.

This experimental protocol was used to study the mechanism by which the fetal LV dramatically increases its output at birth. Previous studies showed that *in utero* oxygen ventilation creates a central circulatory pattern identical with that in the immediate postnatal period (18, 19, 32, 33). The arterial blood gases obtained at a time when the umbilical cord was occluded support the notion that the lungs became the sole site for gas exchange. For this to occur, effective ventilation must have been linked to a significant reduction in pulmonary resistance and increased flow.

As previously shown (18, 19), we also found a marked increase in LV output during *in utero* ventilation. Heart rate changes, which have been suggested to contribute to this increase (34), were not found; rather, we observed a profound increase in LV stroke volume similar to that reported in other studies (18, 19). Associations between the determinants of LV output, *i.e.* contractility, preload, and afterload, and the increase in stroke volume have previously been speculated on.

In this study, contractility as assessed by E_{es} was found not to change at a time when LV output almost doubled. The conventional method of determining E_{es} requires reduction of LV preload, which is usually accomplished by occlusion of the inferior vena cava (35). Application of this technique in the fetus has previously been found to yield inconsistent results (24); the reasons for this were speculated to be related to the unique ventricular interaction and right ventricular dominance of the fetal heart. Because of the difficulties associated with measuring E_{es} using caval occlusions, a single-beat method of estimating E_{es} was used. Although the single-beat E_{es} has not yet been fully validated, the assumption that contractility did not change is supported by the fact that dP/dt_{max} also remained unchanged. The lack of change in dP/dt_{max} despite the marked increase in end-diastolic volume could be interpreted as a decrease in contractility. However, we do not expect this to be the case, because the added demands on the LV with transition would tend to elicit a positive contractile response. We suggest that dP/dt_{max} remained stable more as a result of rightward septal displacement than of free wall distension, a phenomenon observed in human fetuses and infants (36). Therefore, the increase in end-diastolic volume may not have been associated with a comparable degree of free-wall fiber stretching or preload.

Other studies suggested that contractility, as assessed by dP/dt_{max}, fractional shortening, and postextrasystolic potentiation, in lambs studied 18–24 h before delivery and 2–3 h after birth increased significantly (16). Similar findings were reported in the fetal and postnatal lamb heart in intact animals as well as in isolated cardiac muscle (17). Those studies, however, did not examine changes in contractility immediately surrounding the transition. Furthermore, the absence of changes in heart rate during the same period and the previous observation that the transition still occurs in the presence of β-adrenergic blockade (18) imply that no significant sympathetic-driven changes in contractility occur. Although it may be true that substantial changes in contractility do occur during the perinatal period, these do not appear to be essential for the immediate circulatory adjustments at birth.

The marked increase in end-diastolic volume observed in this study may have involved diminution of right ventricular constraint on LV filling. The fetal heart is characterized by RV dominance, with filling pressures equal to or greater than those of the LV (1–3). The LV of the fetus is more ellipsoidal than that of the neonatal child as a result of leftward septal buckling (36). The reduction in RV filling pressure associated with ventilation (32) could result in a change in septal alignment, causing an increase in LV chamber compliance and thus augmenting LV filling. It has also recently been suggested that pressures exerted by tissues surrounding the fetal heart significantly restrict LV filling (37) and that ventilation reduces this constraint (38).

The increase in LV stroke volume observed with ventilation is more than can be ascribed to additional volume loading, because the fetal LV is known to be functioning near the plateau of its Frank-Starling curve (39), although when afterload is controlled LV output can increase in response to increased filling pressures (40). Rather than moving along its cardiac function curve, it is more likely that the ventricle operates on a higher curve, as previously described (18). The significant decrease in E_{aLV}, in addition to a possible increase in LV chamber compliance, might explain such a shift (Fig. 5).

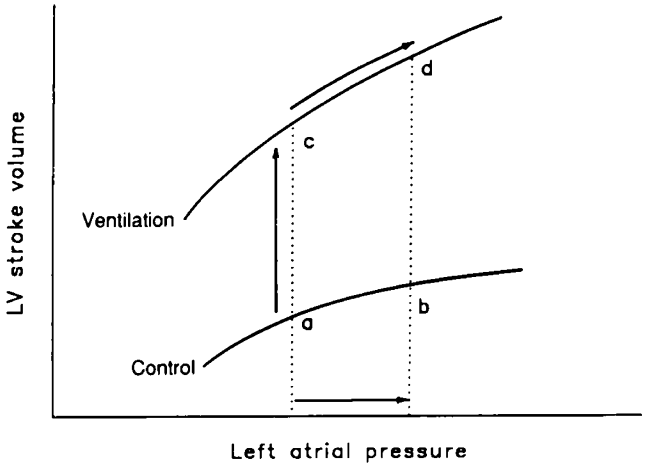

Figure 5. Diagram of LV function curves. In the fetus, the LV is known to operate near the plateau of the curve (*a*), such that increases in atrial pressure (*b*) result in marginal increases in stroke volume. During oxygen ventilation, the decreased afterload and increased compliance cause the LV to operate on an elevated curve (*c*). Because the new curve is steeper, it is possible that the LV gains preload reserve in the process (*d*).

Afterload, expressed as arterial elastance, relates stroke volume to the resulting developed pressure (22, 23). In the fetus, both ventricles eject in parallel into the same arterial system; thus, afterload is a function of the combined stroke volumes and the resulting developed pressure. We hypothesize that the effective afterload that each ventricle encounters is, in part, governed by the volume of blood ejected by the opposite ventricle. At the transition, because the RV no longer contributes to aortic flow, the arterial tree has a larger capacity to be filled by the LV. Thus, the LV is, in effect, exposed to a lower afterload, allowing stroke volume to increase. A further decrease in afterload may be explained by the exposure of the LV to the lower-resistance pulmonary circulation through the ductus arteriosus. A left-to-right shunt through the ductus, accounting for up to 30% of LV output, has been found to exist in the early transitional circulation (11, 41, 42).

The relative contributions of the increase in end-diastolic volume and the decrease in E_{aLV} to augmentation of stroke volume were estimated using PV analysis and were found to contribute equally. The combined effects accounted for the total observed increase in stroke volume, corroborating the finding that contractility did not change. The impact of end-diastolic volume and E_{aLV} on stroke volume did not change after umbilical cord occlusion.

On occlusion of the umbilical cord, afterload increased significantly; however, this response was transient, and after 20 min all hemodynamic effects of the occlusion disappeared. This indicates the possible existence of adaptive vasodilator mechanisms that may also play a role in regulating afterload during transition.

To our knowledge, these are the first reported ejection fractions in the fetus based on absolute volume determinations. Although measurement of absolute LV volume using the conductance catheter may be accurate, the technique has yet to be validated in the fetus. Previous studies using endocardial ultrasonic crystals to measure LV dimensions in fetal sheep reported a fractional shortening of 24.3% (43, 44). Assuming a circular cross section cylindrical geometry, the resulting segmental ejection fraction would have been about 43%, compared with 52.8% calculated in this study. Left ventricular ejection fraction increased with *in utero* ventilation and, because E_{es} was found not to change, this increase must have been due to the reduction in afterload.

All of the increase in LV output in this study occurred with oxygen ventilation alone; occlusion of the umbilical cord caused no further augmentation. This finding is in agreement with previous observations (19) and is also supported by reports that almost the entire decrease in pulmonary vascular resistance, cessation of foramen ovale flow, and most of the ductus arteriosus left-to-right shunt occur with oxygen ventilation before occlusion of the umbilical cord (19, 33).

In summary, this study helps to elucidate the mechanisms by which the fetal LV increases its output at birth. PV analysis revealed that increased end-diastolic volume and reduced effective LV afterload are the major determinants of, and contribute to a comparable extent to, the augmented LV stroke volume. This increase occurs in the absence of any apparent change in LV contractility.

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