The Effects of Hypoxic Acidemia on Left Ventricular End-Systolic Elastance in Fetal Sheep

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ABSTRACT. Using the conductance catheter technique, we measured the effects of hypoxic acidemia on left ventricular end-systolic elastance in anesthetized, 133-d gestation, *in utero* fetal sheep ($n = 7$). Conductance and Millar catheters were introduced into the left ventricle through a carotid artery cutdown. Fetuses were rendered progressively hypoxic and acidemic by placental embolization with repeated injections of $5 \cdot 10^5$ 50- μ m plastic spheres every 15 min via a catheter placed in the fetal abdominal aorta. We recorded pressure-volume data and arterial blood gases at 15-min intervals. End-systolic elastance was computed using a single-beat method of extrapolating maximum isovolumic pressure. A mean of five boluses was required to cause fetal death. Placental embolization caused progressive fetal acidemia. Mean baseline fetal arterial pH was 7.32 ± 0.06 (mean $\pm$ SD) and gradually decreased with embolization ($p < 0.0001$). A linear relationship was found to exist between elastance and pH with a mean decrease of 0.46 kPa/mL per 0.1-unit drop in pH ($r = 0.96$; $p < 0.0001$). Despite the decrease in end-systolic elastance, stroke volume and left-ventricular output were maintained due to a parallel decrease in afterload. The decrease in end-systolic elastance was gradual and extended over the entire clinically important range of pH, rather than being a terminal event. This study, which, to our knowledge, is the first to use the conductance catheter to measure fetal left ventricular function demonstrates that hypoxic acidemia adversely affects myocardial contractility assessed by end-systolic elastance. (*Pediatr Res* 34: 38–43, 1993)

Abbreviations

IVC, inferior vena cava
SVC, superior vena cava
ESPVR, end-systolic pressure-volume relationship
 E_{es} , elastance at end systole (slope of ESPVR)
LV, left ventricle (left ventricular)
 dP/dt_{max} , the maximum of the first time derivative of the ventricular pressure wave form
 P_{max} , peak-developed LV pressure at end-diastolic volume

assessing fetal status during labor. The diagnosis of fetal compromise is based upon the recognition of different fetal heart rate patterns, several of which are nonspecific and often lead to the overdiagnosis of fetal distress. Our aim, as clinicians, is to correctly identify those cases in which hypoxic acidemia is the underlying cause for the heart rate changes. Metabolic acidemia and changes in intracellular pH have been shown to affect myocardial function (1). Indices of cardiac function with the potential to reflect fetal distress more accurately should therefore be investigated.

The present study was devised to examine the effects of hypoxic acidemia on myocardial function in *in utero* fetal sheep. The conductance catheter technique, which has little effect on cardiac mechanics, was used to measure fetal LV volume. E_{es} , the slope of the ESPVR, was measured to assess ventricular contractility. It is a relatively load- and heart rate—insensitive measure of the intrinsic contractile properties of the myocardium (2, 3). This technique has previously been used in the human adult as well as in numerous animal models and age groups (4–6), but this, to our knowledge, is the first application in the fetus. Other more traditional indices of cardiac performance were also correlated with the deteriorating fetal acid-base status induced by progressive placental embolization.

MATERIALS AND METHODS

Surgical procedure. Surgery was performed on seven pregnant ewes with a singleton gestation between 132 and 134 d. Anesthesia was induced with i.v. thiopental sodium and maintained by positive-pressure ventilation with 1 to 1.5% isoflurane and oxygen. The ewes were mildly hyperventilated to prevent CO_2 accumulation. The fetal head and neck were withdrawn through a uterine incision. A 2 F catheter-tip pressure transducer (Millar, Houston, TX) was introduced through the left carotid artery, advanced into the LV, and positioned such that no impact artifact was evident. A 4 F, eight-electrode conductance catheter (made in-house) 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 to the aortic valve. Correct placement of the conductance catheter in the LV was determined by monitoring the segmental volume phase relationships and counterclockwise pressure-volume loop formation. The conductance catheter outer 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 electrode spacing and position were also confirmed at necropsy. A venous line was advanced through the left jugular vein to the right atrium. The fetus was replaced and the uterine incision closed. The hind part of the fetus was then withdrawn through a separate uterine incision, and a fluid-filled catheter was introduced via a femoral artery

Human uteroplacental insufficiency, a known cause of fetal hypoxic acidemia, may lead to the birth of asphyxiated newborns. Electronic fetal heart rate monitoring is the standard method of

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and advanced 10 cm to a position immediately above the abdominal aortic trifurcation. A Fogarty balloon catheter (Baxter, McGaw Park, IL) was introduced through a femoral vein and advanced 18 cm such that the balloon was located in the IVC between the diaphragm and right atrium. Occlusion of the fetal IVC at this level (*i.e.* above the insertion of the ductus venosus) assures a profound reduction upon venous return. In one animal, an additional balloon catheter was also introduced through the left jugular vein to a position in the SVC proximal to the right atrium. The intravascular distance of the femoral catheters was previously established in fetuses of the same gestational age and verified at necropsy. The hind part of the fetus was then replaced and the uterine incision closed. The catheters were exteriorized through the ewe's abdominal incision, which was held closed with clamps. A vascular catheter was placed in the femoral artery of the ewe to monitor maternal blood pressure and gases.

Study protocol. Fetal hypoxic acidemia was gradually induced by embolizing the placenta with injections of $5 \cdot 10^5$ 50- μ m polyethylene microspheres (3M, St. Paul, MN), repeated at 15-min intervals until fetal death occurred. Instantaneous LV pressure-volume loops were monitored and digitally recorded at baseline and before each embolization. Data were acquired at steady state as well as during IVC occlusion. The occlusions were performed by gradually inflating the caval balloon with 0.75 mL of saline over a period of 6 to 8 s. Three IVC occlusions were performed at each level of embolization, full recovery between which was confirmed by return to preocclusion heart rate and LV pressures and volumes. In addition, the effect of SVC occlusion was compared with IVC occlusion in one animal. After hemodynamic recordings, fetal arterial blood samples (0.4 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. Because acidosis affects the electrical resistance of blood, this parameter was also determined at each interval using a 4-mL cuvette connected to a modified Sigma-5 signal conditioner (Leycom, Oesgsteest, The Netherlands). This blood was returned to the fetus.

Data acquisition and analysis. The principles and technique of the conductance catheter method of LV volume estimation are described in detail elsewhere (4-7). Briefly, the conductance catheter was connected to the Sigma-5 unit, which applied an excitation current (30 μ A, 20 kHz) to the outer electrodes and measured the five segmental conductances, G_i , between intervening electrode pairs. Total time-varying conductance, $G(t)$, was estimated as the algebraic sum:

$$G(t) = \sum_{i=1}^5 G_i + \frac{G_l}{3}$$

where $\frac{1}{3}$ term approximates the conductance of blood within the conic apical region not actually being measured by the catheter. The instantaneous LV volume, $V(t)$, is then obtained by:

$$V(t) = \frac{1}{\alpha} (L^2 \cdot \rho \cdot G(t) - \alpha V_c)$$

where α is a unitless, empirical coefficient relating conductance catheter-derived stroke volume to that obtained by some other method (*i.e.* "gold standard"). In this study, α was assumed to be 1. L is the interelectrode spacing, and ρ is the specific electrical resistance of blood as measured with the rho cuvette. 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 the method of dilution (4), whereby the conductivity of blood was transiently altered by bolus injection of 0.5 mL of 3 M NaCl into the right atrium without affecting systolic pressure. LV pressure, five segmental conductances, and ECG were digitized (250 Hz, 12 bit) by an IBM AT compatible microcomputer and stored on hard disk for subsequent analysis

using software developed at The Toronto Hospital for Sick Children.

E_{es} was computed by two methods. The first of these used transient balloon occlusion of the IVC to modulate preload. This generated a family of pressure-volume loops over a range of loading conditions (Fig. 1). Linear regression of the end-systolic pressure-volume coordinates (maximal ratio of pressure to volume), yielded a first approximation of the ESPVR and an initial volume intercept V_0 , the unstressed ventricular volume. E_{es} was then computed using the time-varying model (8):

$$E(t) = \frac{P(t)}{V(t) - V_0(t)}$$

This yielded a new estimate of V_0 , which was subsequently used in recomputing E_{es} . The iterations were repeated until the difference between the new value for V_0 and its previous value was <0.1 mL.

The second method of computing E_{es} was by analysis of pressure-volume loops under steady state loading conditions. Knowing the P_{max} of an isovolumic (nonejecting) contraction at end-diastolic volume (V_{ed}) can allow determination of E_{es} from a single cardiac cycle. If the ESPVR of an ejecting ventricle is equivalent to that generated by the same ventricle beating isovolumically, E_{es} will be the slope of the line connecting the end-systolic pressure-volume coordinate and the P_{max} - V_{ed} point (Fig. 2), or

$$E_{es} = \frac{P_{max} - P_{es}}{V_{ed} - V_{es}}$$

The pressure wave form of an isovolumic LV beat has previously been shown to follow a sinusoidal trajectory (9, 10). Ejecting and isovolumic beats are identical from the onset of contraction to the time of dP/dt_{max} , which normally occurs before the opening of the aortic valve (Fig. 3). Although the duration, or period (T), of an isovolumic beat (*i.e.* the time from onset of contraction to the end of active relaxation) is typically longer than that of an ejecting beat, the contraction phases of both beats are of similar length. Based on these observations, a mathematical model was developed to predict P_{max} . As the isovolumic pressure can be described by a sine, its angular derivative corresponds to a cosine of the same amplitude. Thus, the amplitude of $dP/d\theta$, which is simply dP/dt (kPa/mL) converted to angular units (kPa/radian), is equivalent to that of the isovolumic pressure wave form. This identity is applied to estimate P_{max} from the pressure data of an ejecting beat by:

$$P_{max} = \frac{dP/dt_{max} \cdot T}{2\pi} + P_{dc}$$

where P_{dc} is the vertical offset of the pressure wave form, the pressure at which dP/dt_{max} occurs. The period of the extrapolated, nonejecting cycle is known because the time from dP/dt_{max} to

Fig. 1. Fetal LV pressure-volume loops obtained during an IVC occlusion.

Fig. 2. Schematic diagram illustrating how the ESPVR is determined from a single cardiac cycle. P_{max} is the extrapolated peak isovolumic pressure developed at end-diastolic volume (V_{ed}). E_{es} is the slope of the line joining that point with the end-systolic pressure-volume coordinate (P_{es} , V_{es}); V_o is the volume axis intercept or the unstressed ventricular volume.

Fig. 3. Temporal representation of the ejecting pressure, dP/dt , and the corresponding isovolumic pressure of a single cardiac cycle. Ejecting and isovolumic pressures are similar during the initial phase of contraction. The end of contraction of both beats essentially coincide.

the end of contraction is the same in both ejecting and isovolumic beats and occupies $1/4T$ of the isovolumic cycle. We tested this method in experiments in which the intact hearts of eight pigs were made to beat isovolumically by sudden tightening of a snare around the aorta. A linear relationship ($n = 16$, slope 1.08, $r = 0.96$) was found to exist between the observed peak isovolumic pressure and that predicted from ejecting beats (10).

LV stroke volume and heart rate were measured, and LV output was computed for the baseline state and before each bolus injection. In addition, dP/dt_{max} was measured at each state and normalized to the baseline heart rate. Afterload was assessed by measuring arterial elastance, the ratio of end-systolic pressure to stroke volume (11, 12).

Each value given represents an average of 20 consecutive cardiac cycle measurements, taken immediately preceding each microsphere bolus injection.

Statistical analysis. Analysis of variance with repeated measures was used to determine the significance of changes in blood gas values with placental embolization. The relationships be-

tween hemodynamic indices and pH were determined by multiple regression analysis, with dummy variables using effects coding. This approach takes into account the wide interanimal variability of values, such that only within-fetus differences are considered in the statistical analysis (13). As an estimate of between-fetus variability of each hemodynamic parameter, the mean and SD of the dummy variable coefficients were computed. Significance was assumed at the $p < 0.05$ level.

This study was approved by the hospital animal care committee following the guidelines of the Canadian Council for Animal Care.

RESULTS

A mean of five (range four to six) microsphere boluses were required to cause fetal death. Placental embolization caused progressive fetal asphyxia (Fig. 4). Mean baseline fetal arterial pH was 7.32 ± 0.06 and progressively decreased with embolization ($p < 0.0001$). The mean baseline P_{CO_2} was 7.01 ± 1.78 kPa, gradually increasing with embolization ($p = 0.01$). The mean baseline P_{O_2} was 2.73 ± 0.37 kPa and progressively decreased with embolization ($p < 0.01$).

The results of multiple linear regression analyses relating the individual hemodynamic parameters to pH are summarized in Table 1. Baseline heart rate was 180 ± 35 beats per min, LV stroke volume was 2.74 ± 1.04 mL, and LV output was 441.1 ± 219.6 mL/min. These values did not change with placental embolization. End-systolic pressure, and therefore afterload, as measured by arterial elastance (Fig. 5), decreased significantly with pH.

At each level of embolization, E_{es} , as assessed by single-beat analysis, was reproducible when applied to 20 consecutive cardiac cycles with coefficients of variation ranging from 0.02 to 0.06. E_{es} decreased significantly with pH (Fig. 6). The drop in pH caused a decrease in dP/dt_{max} that was even greater and more significant when dP/dt_{max} was normalized for heart rate (Fig. 7).

Measurement of E_{es} using the IVC occlusion technique yielded inconclusive results. Although highly linear ESPVR were obtained for each occlusion, E_{es} could not be reliably determined, because values varied significantly between the three occlusions performed at each level of embolization. Although all IVC occlusions resulted in a decrease in end-diastolic volume, some pressure-volume loops exhibited a paradoxical increase in stroke volume (Fig. 8). It was, therefore, not possible to correlate this measure with pH. In the one animal in which the SVC was occluded, values of E_{es} measured by the iterative method were found to be in line with those obtained by steady state analysis ($r = 0.99$; coefficient of variation = 0.06).

Although the injection of hypertonic NaCl into the right atrium had an immediate effect of the LV volume signal, mixing was deemed adequate because all segments showed a simultaneous response lasting several beats. However, it is most likely that, of the saline injected into the right atrium, only a small fraction entered the LV through the foramen ovale. The remainder went to the right ventricle, thus altering the parallel conductance due to the right ventricular blood pool. For this reason, we elected not to include results based on absolute volume determinations in this study.

DISCUSSION

The conductance catheter method has become a well-established technique of measuring instantaneous LV volume in the intact adult heart. Recently, this method has been validated in newborn piglets (14), the size of which is comparable to that of near-term fetal sheep. Combining conductance catheter volumes with a simultaneous LV pressure facilitates the computation of E_{es} , a relatively load-independent index of contractility.

The conventional method of measuring E_{es} requires preload modulation using IVC occlusions. Several mechanisms may

Fig. 4. Changes in blood gases that occurred with placental embolization in seven fetal sheep.

Table 1. Results of multiple linear regression analyses for hemodynamic variables*

	b	SEM	p	Lower CI	Upper CI	r	χ	SD
Heart rate (bpm)	-5.55	3.88	>0.16	-13.47	2.45	0.59	-0.54	21.22
LV stroke volume (mL)	0.01	0.05	>0.89	-0.10	0.12	0.95	0.07	1.36
LV output (mL/min)	-16.55	15.07	>0.28	-47.41	14.27	0.92	11.19	296.26
End-systolic pressure (kPa)	0.82	0.11	<0.0001	0.59	1.05	0.92	2.07	16.22
Arterial elastance (kPa/mL)	0.27	0.07	<0.0006	0.13	0.41	0.97	1.06	19.10
E_{es} (kPa/mL)	0.46	0.06	<0.0001	0.33	0.58	0.96	0.93	12.40
dP/dt_{max} (kPa/s)	21.09	4.35	<0.0001	12.20	29.97	0.91	66.02	624.50
dP/dt_{max} normalized (kPa/s)	24.17	2.86	<0.0001	18.33	30.01	0.97	68.37	772.10

* All coefficients, b, the slopes of the relationship of each dependent variable to pH, are given in their respective units per 0.1 unit change in pH. The p values represent the significance of the effect of pH on the dependent variables. Lower and upper CI are the 95% confidence intervals. An estimate of the between-fetus variability is given by χ and SD of the six fetal coefficients.

underlie the nonrepeatability of measurements obtained by this method in our study. The observation that SVC occlusions yielded similar elastances to steady state analysis is most likely coincidental. In the absence of autonomic blockade, the variability in E_{es} may have resulted from reflex activation of baroreceptors and fluctuations in catecholamine levels. Another possible explanation may be provided by the unique ventricular interaction characteristic of the fetal heart. In the fetus, the dominant right ventricle operates at systemic pressures and provides about 2/3 of the combined ventricular output. By decreasing venous return and right ventricular filling, septal compression of the LV space may be reduced. If this effect is not linearly correlated with the decrease in LV volume during IVC occlusions, the resulting pressure-volume relationships may be irregular. In addition, the proportion of blood passing through the foramen ovale may be variably affected by IVC occlusion, further confounding the LV ESPVR. It is also possible that the decrease in right ventricular volume during IVC occlusion is associated with a reduction in parallel conductance, which would be most pronounced at the end of ejection, thus causing underestimation of LV end-systolic volume. This may be the reason for the occasional atypical appearance of the pressure-volume loops

during IVC occlusions (Fig. 8), in which stroke volume paradoxically appeared to be increasing during preload reduction. The relative contributions of these mechanisms to the error in determination of LV E_{es} by IVC occlusion using the conductance catheter technique in fetal lambs remains to be determined.

Another method of measuring E_{es} , which does not require load modulation, is gaining acceptance. Sunagawa *et al.* (9) introduced a technique of estimating P_{max} that exploits the sinusoidal behavior of isovolumic pressure wave forms. These investigators applied a nonlinear regression to fit the isovolumic contraction and relaxation phases of the pressure wave form of ejecting beats to a mathematical model describing a nonejecting beat. A good correlation between single-beat elastance using the method of Sunagawa *et al.* and that generated by IVC occlusion has been reported in dogs (15) and in humans (16). This formulation, however, is deficient because it ignores the asymmetry of the pressure wave form of the ejecting contractions. In addition, the abbreviation of ejecting relative to isovolumic beats was overlooked. The method used for the determination of P_{max} in the current study involves only the isovolumic contraction phase of the ejecting beat, the only segment that is identical to that of a nonejecting beat. The relaxation phase of an ejecting beat bears

Fig. 5. Pressure-volume loops from one fetal sheep showing arterial elastance (the slope of the dotted lines) at baseline (a) and before the 5th placental embolization (b). The reduction in afterload is depicted by the decreased arterial elastance.

Fig. 6. Changes in fetal LV end-systolic elastance (E_{es}), associated with the change in arterial pH. Solid lines depict regression slopes for individual animals. The dotted line indicates the mean slope for seven animals.

Fig. 7. Changes in fetal LV dP/dt_{max} , normalized for heart rate, associated with the change in arterial pH. Solid lines depict regression slopes for individual animals. The dotted line indicates the mean slope for seven animals.

Fig. 8. Fetal LV pressure-volume loops obtained during an IVC occlusion, showing a paradoxical increase in stroke volume with decrease in preload.

little resemblance to that of an isovolumic beat. Although Sunagawa *et al.* defined the period of the isovolumic beat as the time from end-diastole to the time when pressure returns to that value, this does not take into consideration the higher amplitude and the slower relaxation rate of the isovolumic beat. Our method overcomes this underestimation of the period by not constraining it to that of the ejecting beat. In contrast to the IVC occlusion method, steady state analysis proved to be highly reproducible.

Another issue that merits attention when the conductance catheter technique is applied to the fetus relates to the measurement of parallel conductance. In the adult model, when the bolus injection of hypertonic NaCl is given, a delayed response in the LV conductance signal is usually observed due to the time required to pass through the pulmonary circulation. This delay, encompassing several beats, allows adequate mixing with blood. In the fetus, the foramen ovale allows almost immediate shunting of a portion of the saline from the right atrium to the left heart. This did not impede adequate mixing, as indicated by uniform segmental volume changes, which is required for proper determination of parallel conductance. The saline entering the right ventricle may, however, have introduced error in the determination of absolute volumes. Because of this possible limitation, absolute volumes were not considered in this study. In future studies, this limitation may be overcome by injecting the saline directly into the pulmonary artery through a Swan-Ganz catheter, although this could significantly complicate the instrumentation. The possibility of an alternative solution has arisen from observations made in a more recent study. After saline injection into the right atrium, the volume signal beyond the immediate response due to shunting through the foramen ovale was monitored. A second, delayed increase in the LV volume signal due to pulmonary venous return was observed (unpublished observations). This second response could be used to compute parallel conductance, thus avoiding the influence of saline on right ventricular conductivity.

There was a progressive decrease in LV contractility, as determined by E_{es} , associated with deepening fetal hypoxic acidemia. This decrease in elastance was gradual and extended over the entire clinically important pH range, rather than being a terminal event. This is in agreement with findings of Teplinsky *et al.* (19), who studied the effect of lactic acidemia, and Walley *et al.* (20), who investigated the effects of respiratory acidosis on LV function in adult dogs. Both studies found that LV elastance decreased with pH. Our findings in the intact heart are also in concordance with the observation that changes in intracellular pH adversely affect myocardial function (1).

In other studies, fetal hypoxemia with or without acidemia was created by interventions such as the induction of maternal hypoxemia, occlusion of the uterine or umbilical circulations, or the direct infusion of acid into the fetal circulation. Clinically,

maternal hypoxemia is very uncommon as a cause for fetal asphyxia. Furthermore, fetal asphyxia is a gradually progressive condition, where acidemia is paralleled by tissue acidosis. The intravascular administration of acid is not accompanied by CO₂ accumulation, and the degree of tissue acidosis generated by this intervention, especially myocardial tissue acidosis that affects contractility, might not accurately reflect clinical asphyxia. We have previously shown that embolization of the fetal placenta in sheep results in a gradually deepening hypoxic acidemia (21) and have thus decided to use this method in the current study.

When metabolic acidemia was induced by HCl infusion in unanesthetized newborn lambs, it caused a significant decrease in LV dP/dt_{max} from 410.56 ± 20.80 kPa/s at pH 7.42 to 246.60 ± 25.1 kPa/s at pH 7.11 (22). Similar findings were reported when lactic acidemia was induced in adult dogs: LV dP/dt_{max} decreased from 270.73 ± 91.40 kPa/s at pH 7.4 to 228.20 ± 68.50 kPa/s at pH 7.1 (19). We found a similar decrease in LV dP/dt_{max} . It should, however, be noted that dP/dt_{max} is not a pure measure of contractility because it is also influenced by factors such as heart rate and preload. Isoflurane may have caused fetal myocardial depression; nevertheless, this anesthetic has only minimal cardiovascular effects in the adult and in the fetus when used in low concentrations, as in our study (23, 24), so we suspect this effect to be small.

When previously studied, hypoxemia was found not to affect fetal LV stroke volume (25, 26), which is in agreement with our observations. Our finding of a gradual reduction in afterload provides an explanation for the mechanism by which the LV is able to maintain its stroke volume despite a decrease in contractility. A decrease in afterload has previously been associated with acidosis in adult dogs (20). Once complicated by acidemia, combined (25, 26) or individual (27) ventricular output in chronically instrumented fetal sheep decreases, mainly as a result of bradycardia. In this study, heart rate and LV output were maintained. This is in accordance with the previously described observation that, in acute experiments on fetal sheep, the bradycardic effect of hypoxia was negated by activation of aortic chemoreceptors (28).

In conclusion, this study, which used the conductance catheter technique for the assessment of fetal ESPVR, demonstrated tight coupling of fetal acid-base balance and LV contractility. Furthermore, the correlation between pH and E_{es} extended over the entire range of clinical importance. These observations suggest that indices of myocardial function should be explored as a means of improving upon the diagnostic accuracy currently provided by fetal heart rate monitoring.

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