Metabolic acidosis decreases fetal myocardial isovolumic velocities in a chronic sheep model of increased placental vascular resistance

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Acharya G, Räsänen J, Mäkikallio K, Erkinaro T, Kavasmaa T, Haapason M, Mertens L, Huhta JC. Metabolic acidosis decreases fetal myocardial isovolumic velocities in a chronic sheep model of increased placental vascular resistance. Am J Physiol Heart Circ Physiol 294: H498–H504, 2008. First published November 16, 2007; doi:10.1152/ajpheart.00492.2007.—We hypothesized that acute fetal metabolic acidosis decreases fetal myocardial motion in a chronic sheep model of increased placental vascular resistance (R\textsubscript{ua}). Eleven ewes and fetuses were instrumented at 118–122 days of gestation. After 5 days of recovery and 24 h of placental embolization to increase R\textsubscript{ua}, longitudinal myocardial velocities of the right and left ventricles and interventricular septum (IVS) were assessed at the level of the atrioventricular valve annuli via tissue Doppler imaging (TDI). Ventricular inflow (E and A waves) and outflow velocities were obtained, and cardiac outputs were calculated. All measurements were performed at baseline and during fetal acidosis caused by epidural anesthesia-induced maternal hypotension, which decreased uterine artery volume blood flow, fetal oxygenation, arterial pH, and base excess and increased lactate. Compared with baseline, the peak isovolumic myocardial contraction and relaxation velocities of the ventricles and IVS, early relaxation velocity (E\textsuperscript{e}) of the ventricles, and systolic velocity of the IVS decreased during metabolic acidosis. The proportion of isovolumic contraction time of the cardiac cycle increased but the isovolumic relaxation and ejection time proportions remained unchanged compared with baseline. In sheep fetuses with increased R\textsubscript{ua} and acute metabolic acidosis, global cardiac function was preserved. However, acute metabolic acidosis impaired myocardial contractility during the isovolumic phase and relaxation during the isovolumic and early filling phases of the cardiac cycle.

METHODS

Measurements were made on 11 Finnish pregnant sheep (gestational age 123–127 days, full-term 145 days) that were part of a research protocol investigating fetomaternal cardiovascular function in a model of increased R\textsubscript{ua}. All experiments were performed in accordance with the guidelines of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986) and in compliance with European Union Directive 86/609/EEC (1997). The research protocol was approved by the Animal Care and Use Committee of the University of Oulu.

Surgical procedure and instrumentation. After they were fasted overnight, the sheep were premedicated intramuscularly with ketamine (2 mg/kg) and midazolam (0.2 mg/kg). Venous access was obtained by cannulation of an auricular vein. General anesthesia was induced with propofol (4–7 mg/kg iv). Anesthesia was maintained with isoflurane (1–2.5%) in an oxygen-air mixture delivered via an endotracheal tube; intravenous boluses of fentanyl were administered as required. A catheter was inserted into the ewe’s external left jugular vein to serve as a permanent intravenous line, and an auricular artery was cannulated for blood pressure (BP) and heart rate monitoring. Mechanical ventilation was maintained throughout the surgical procedure.

A midline laparotomy was performed, and a 6-mm transit-time ultrasonic flow probe (Transonic Systems, Ithaca, NY) was placed around the uterine artery supplying the pregnant uterine horn. There-

IN RESPONSE TO HYPOXEMIA, fetuses generally redistribute more blood toward the myocardium, brain, and adrenal glands at the expense of the lower body and viscera (3, 22). The fetal heart is known to have a remarkable ability to withstand hypoxia (10, 30), but progressive hypoxia and acidosis may decrease blood supply to the heart (6) and alter myocardial energy metabolism (18, 40). However, despite reduced myocardial contractility, global cardiac function is preserved during moderate acidemia (26). Echocardiography has been applied to assess fetal cardiac function noninvasively in a variety of clinical conditions, such as intrauterine growth restriction (29), hydrops (17), congenital heart disease (38), and twin-twin transfusion syndrome (36). Recently, tissue Doppler imaging (TDI) of myocardial motion has been introduced in clinical practice as a promising new technique in the assessment of fetal heart function (2, 8, 11, 15, 32, 34).

In human pregnancies, placental insufficiency with increased placental vascular resistance (R\textsubscript{ua}) can lead to fetal metabolic acidosis and death. Our experiments in a chronic sheep model of increased R\textsubscript{ua} were designed to test the hypothesis that acute metabolic acidosis decreases fetal myocardial motion. We asked the following questions. 1) How does the fetal myocardium tolerate metabolic acidosis? 2) Does acute metabolic acidosis with increased R\textsubscript{ua} affect longitudinal myocardial wall motion and TDI parameters describing cardiac function?

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after, the fetal lower body was exposed through a small incision on the anterior uterine wall. Polyurethane catheters (18 gauge) were inserted into the fetal descending aorta and inferior vena cava via the femoral artery and vein, respectively. A small transverse incision was made on the umbilical arteries and secured to the fetal abdomen just below the umbilical cord insertion, and the umbilical arteries were exposed. A 4-mm transit-time ultrasonic flow probe (Transonic Systems) was placed around the umbilical arteries and secured to the fetal abdomen. Then the fetus was returned to the uterine cavity, the lost amniotic fluid was replaced with warm 0.9% NaCl, and the hysterotomy and laparotomy incisions were closed. The catheters and flow probes were tunneled subcutaneously and exteriorized through a small skin incision and secured to the ewe’s flank.

For postoperative analgesia, a fentanyl patch was attached to the ewe’s tail, and intramuscular fentanyl (2 μg/kg) was given in the first 48 h and buprenorphine (0.01 mg/kg) thereafter. The ewes were intravenously infused with 1 liter of Ringer lactate solution and 1 g of ampicillin daily and the fetuses with 1 × 10⁶ U of benzyl penicillin daily.

In human pregnancies complicated by placental insufficiency and increased placental vascular impedance, the number of small tertiary villi arterioles is significantly reduced (12). To simulate this pathophysiological condition, we chose to embolize the placenta on postoperative day 4 with 45- to 150-μm microspheres (Contour Emboli, Target Therapeutics, Fremont, CA). A dry volume of 0.25 ml of microspheres was suspended in 0.5 ml of 20% albumin and diluted with 10 ml of 0.9% NaCl. This solution was injected into the fetal descending aorta via the femoral artery catheter in 1-ml increments every 15 min until fetal arterial oxygen saturation decreased by 30% from preembolization values.

### Data acquisition
Data were acquired from anesthetized animals on postoperative day 5, ~24 h after placental embolization. General anesthesia was induced with propofol (4–7 mg/kg iv) and maintained with isoflurane (1–1.5%) in a 40% oxygen-air mixture delivered via an endotracheal tube. Rocuronium (20 mg) was used for muscle relaxation to facilitate mechanical ventilation. Tidal volume was adjusted to 8–10 ml/kg and respiratory rate to 18 min⁻¹.

A 16-gauge polyurethane catheter was inserted into the descending aorta of the sheep via a femoral artery for monitoring aortic BP. In addition, a 19-gauge epidural catheter was placed into the epidual space just above the lumbosacral junction. Ringer lactate solution was infused at a fixed rate of 200 ml/h through the external jugular vein access. The sheep was positioned supine with a right lateral tilt. The animals were allowed to stabilize for 30 min before the baseline measurements were made.

Fetal metabolic acidosis was induced by reduction of uterine artery volume blood flow (Qutra). Bupivacaine (0.5%) was administered through the epidural catheter to a total dose of 0.3 ml/kg maternal body wt 2 min after an initial test dose of 5 ml, and hypotension was allowed to develop to a ≈20% decrease in maternal systolic BP. The criteria for fetal metabolic acidosis were as follows: arterial pH <7.20, base excess less than −6 mmol/l, and lactate >6 mmol/l.

The aortic BP and central venous pressure (CVP) of the ewe and the fetus were continuously monitored using disposable pressure transducers (model DT-XX, Ohmeda, Hatfield, UK). Pressure transducers were first zeroed against the atmospheric pressure and then calibrated using a 150-cm intravenous line filled with water. Pressure of 150 cmH₂O is equivalent to 110 mmHg. Mean arterial pressure (MAP) was calculated as follows: MAP = diastolic BP + 1/3(systolic BP – diastolic BP). Qutra and umbilical artery volume blood flow (Qutra) were measured directly with perivascular transit-time ultrasonic flow probes (model T206, Transonic Systems). Rutra was calculated as follows: Rutra = fetal MAP/Qutra. All these variables were recorded continuously at a sampling rate of 100 Hz using a polygraph (model U1100A, Biopac Systems, Santa Barbara, CA) and computerized data acquisition software (Acqknowledge version 3.5.7 for Windows, Biopac Systems).

Ultrasonography was performed using the Vivid 7 Dimension ultrasound system (GE Vingmed Ultrasound, Horten, Norway) with a 10-MHz phased-array transducer. Ventricular inflow and outflow blood velocity waveforms were obtained using pulsed Doppler ultrasonography, with the insonation angle maintained at <15°. Time-velocity integrals of pulmonary and aortic valve blood velocity waveforms were measured by planimetry of the area underneath the Doppler spectrum. Pulmonary and aortic valve diameters were obtained to calculate their cross-sectional areas (CSA). Right and left ventricular cardiac outputs were calculated (Q = time-velocity integral × CSA × fetal heart rate) (37). The longitudinal velocities of the right ventricle (RV), left ventricle (LV), and interventricular septum (IVS) during the cardiac cycle were assessed using pulsed-wave TDI, with the sample volume (1–1.5 mm) placed at the level of the aortoventricular valve annuli and aligned as parallel as possible to the myocardial wall (<15° angle of insonation). Myocardial velocities were recorded during three to six cardiac cycles at a sweep speed of 100 mm/s. All measurements were performed at baseline and during fetal metabolic acidosis by a single investigator.

### Table 1. Results of arterial blood gas analysis and acid-base status of sheep fetuses before placental embolization, at baseline, and during metabolic acidosis

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>Arterial PO₂, mmHg</th>
<th>Arterial PCO₂, mmHg</th>
<th>BE, mmol/l</th>
<th>Lactate, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preembolization</td>
<td>7.32±0.04</td>
<td>23.5±3.5</td>
<td>49.2±5.0</td>
<td>−2.0±2.7</td>
<td>1.6±0.6</td>
</tr>
<tr>
<td>Baseline</td>
<td>7.27±0.07</td>
<td>19.6±4.3</td>
<td>55.6±7.5</td>
<td>−1.0±0.6</td>
<td>3.1±1.6</td>
</tr>
<tr>
<td>Acidosis</td>
<td>7.04±0.13*</td>
<td>14.4±4.8*</td>
<td>72.1±16†</td>
<td>−11.0±4.14*</td>
<td>9.8±2.1*</td>
</tr>
</tbody>
</table>

Values are means ± SD (n = 11). BE, base excess. *P < 0.0001; †P = 0.002; ‡P = 0.004 vs. baseline.
MYOCARDIAL VELOCITIES IN FETAL ACIDOSIS

Fig. 2. Longitudinal myocardial velocities obtained at the level of the mitral valve annulus from sheep fetuses during tachycardia (A) and bradycardia (B). Note merged E' and A' waves (i.e., monophasic relaxation) in A and widely spaced E' and A' waves in B. Trace is oriented from an apical view, such that systolic deflections (S') are above the zero line and toward the transducer.

Tissue Doppler traces were analyzed offline using EchoPac PC software (version 6.0.0, GE Medical Systems). Maximal myocardial velocities were measured during isovolumic relaxation (IVRV), early ventricular filling (E'), atrial contraction (A'), isovolumic contraction (IVCV), and ventricular systole (S'). The slopes of isovolumic myocardial acceleration and deceleration were calculated by dividing the peak IVCV and IVRV by the time intervals from the onset to the peak of these velocity waveforms, respectively. Ventricular and septal isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), ejection time (ET), and the total duration of the cardiac cycle were measured using pulsed-wave tissue Doppler traces (Fig. 1). The TDI Tei index (41) was calculated by dividing the sum of IVCT and IVRV by ET.

Fetal arterial blood samples were analyzed for acid-base status (corrected for 39°C) using an i-Stat 1 analyzer (i-Stat, East Windsor, NJ). At the end of the experiment, the animals were euthanized with a lethal dose of pentobarbital sodium.

Data were analyzed using Statistical Software for Social Sciences for Windows version 14.0 (SPSS, Chicago, IL). For continuous parametric variables, the paired t-test was used to examine differences between baseline and acidosis. Correlations were tested using the Pearson correlation coefficient. Statistical significance was set at \( P \leq 0.05 \).

RESULTS

The mean weight of the ewes (\( n = 11 \)) was 56 (range 49–61) kg. The mean gestational age on the day of the experiment was 125 (range 123–127) days, and the mean fetal weight was 2,190 (range 1,220–2,675) g. During hypotension, maternal MAP (87 ± 8 vs. 65 ± 14 mmHg, \( P < 0.0001 \)) and \( Q_{\text{fetal}} \) (472 ± 223 vs. 223 ± 141 ml/min, \( P = 0.004 \)) were reduced compared with baseline. \( Q_{\text{fetal}} \) (89 ± 32 vs. 58 ± 39 ml·kg\(^{-1}\)·min\(^{-1}\), \( P = 0.01 \)) decreased, while the fetal heart rate (151 ± 35 vs. 158 ± 25 beats/min, \( P = 0.533 \)), MAP (50 ± 8 vs. 47 ± 7 mmHg, \( P = 0.245 \)), and CVP (14 ± 6 vs. 15 ± 7 mmHg, \( P = 0.339 \)) remained unchanged. During maternal hypotension, \( R_{\text{fetal}} \) (0.291 ± 0.102 vs. 0.402 ± 0.114 mmHg·ml\(^{-1}\)·min\(^{-1}\), \( P = 0.007 \)) was increased compared with baseline. The results of fetal arterial blood gas analysis and acid-base status are presented in Table 1.

It was possible to obtain good-quality images of pulsed-wave tissue Doppler recordings of the longitudinal myocardial velocities of the RV, LV, and IVS in all cases by transabdominal echocardiography. Typically, the TDI waveform recordings showed IVCV, S', IVRV, E', and A' waves (Fig. 1). However, in some fetuses, we observed monophasic myocardial relaxation velocity (fused E' and A' waves) during tachycardia (Fig. 2A) and a prolonged period of myocardial quiescence between the early relaxation phase and the atrial contraction phase of diastole (widely separated E' and A' waves) during bradycardia (Fig. 2B).

Fetal myocardial TDI parameters obtained from the LV, RV, and IVS at the level of the atrioventricular valve annuli during baseline and metabolic acidosis are shown in Tables 2, Tables 3, and Tables 4, respectively. The TDI parameters were not significantly different between the two ventricles. Compared with baseline, the peak IVCV, IVRV, and the slopes of isovolumic myocardial acceleration and deceleration of the ventricles and IVS decreased significantly during fetal acidosis (Fig. 3). The peak early relaxation (E' wave) velocity of both ventricles and the peak systolic (S') velocity of the IVS also decreased significantly during acidosis. During fetal acidosis, the proportion of IVCT of the cardiac cycle (IVCT%) increased but the Tei index did not change significantly from the baseline value for both ventricles as well as the IVS. The E-to-E' ratio (E/E') for both ventricles was significantly higher during acidosis than at baseline.

The peak IVCV, IVRV, and the slopes of isovolumic myocardial acceleration and deceleration of the LV, RV, and IVS correlated significantly with fetal pH, except the RV peak

Table 2. TDI parameters of fetal left ventricle at the level of the mitral valve annulus

<table>
<thead>
<tr>
<th></th>
<th>S', cm/s</th>
<th>E', cm/s</th>
<th>A', cm/s</th>
<th>IVCV, cm/s</th>
<th>IVRV, cm/s</th>
<th>Accel, cm/s²</th>
<th>Decel, cm/s²</th>
<th>E/E'</th>
<th>IVRT, %</th>
<th>IVCT, %</th>
<th>ET, %</th>
<th>Tei Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.7±2.0</td>
<td>7.7±1.3</td>
<td>12.8±3.0</td>
<td>6.1±2.3</td>
<td>4.0±0.9</td>
<td>628±231</td>
<td>357±88</td>
<td>5.21±1.3</td>
<td>14.0±6.8</td>
<td>8.1±3.1</td>
<td>36±6.9</td>
<td>0.61±0.16</td>
</tr>
<tr>
<td>Acidosis</td>
<td>7.5±1.1</td>
<td>6.2±1.3</td>
<td>11.7±2.4</td>
<td>4.3±1.8</td>
<td>2.6±0.7</td>
<td>305±97</td>
<td>205±61</td>
<td>7.74±1.3</td>
<td>13.5±3.8</td>
<td>10.7±3.8</td>
<td>38±4.3</td>
<td>0.65±0.16</td>
</tr>
<tr>
<td>( P )</td>
<td>0.096</td>
<td>0.022</td>
<td>0.364</td>
<td>0.006</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.007</td>
<td>0.827</td>
<td>0.047</td>
<td>0.450</td>
<td>0.445</td>
</tr>
</tbody>
</table>

Values are means ± SD. TDI, tissue Doppler imaging; S', systolic contraction velocity; E', early diastolic relaxation velocity; A', velocity during atrial contraction; IVCV, isovolumic contraction velocity; E, ventricular inflow velocity during early filling; IVRV, isovolumic relaxation velocity; Accel, isovolumic myocardial acceleration; Decel, isovolumic myocardial deceleration; IVRT, isovolumic relaxation time; IVCT, isovolumic contraction time; ET, ejection time.
IVRV. The LV and IVS Tei indexes correlated significantly with fetal pH, but the RV Tei index did not (Table 5). When we examined the relationships between the increase in $R_{ua}$ from baseline to the acidosis phase ($\Delta R_{ua}$) and TDI parameters, only $\Delta$ IVS IVCT% ($r = 0.65$, $P < 0.031$) and $\Delta$ IVS Tei index ($r = 0.64$, $P < 0.034$) showed significant correlations.

The fetal LV (412 ± 178 vs. 449 ± 199 ml/min, $P = 0.511$), RV (584 ± 283 vs. 588 ± 300 ml/min, $P = 0.971$), and LV + RV (996 ± 454 vs. 1,037 ± 449 ml/min, $P = 0.791$) cardiac outputs during acidosis were comparable with baseline values.

## DISCUSSION

With our experimental animal model, we have tried to replicate the pathophysiological situation in human placental insufficiency, in which placental dysfunction can lead to fetal acidosis and death. Fetal hypoxia and acidosis can be induced by maternal hypoxemia (35) or a reduction in $Q_{ua}$ (19) and $Q_{ma}$ (23). Our experiments in a sheep model of increased $R_{ua}$ were designed to study fetal myocardial function during acute metabolic acidosis induced by a reduction of $Q_{ma}$. We used TDI-derived longitudinal myocardial velocities and cardiac cycle time intervals to infer information on fetal cardiac function.

Myocardial contractility was assessed by the slope of isovolumic myocardial acceleration, which is independent of cardiac loading conditions (42, 43). Other indexes describing cardiac systolic function included peak IVCV, IVCT%, and peak $S'$ wave velocity. Prejection indexes are less influenced by afterload than ejection phase indexes (27). The slope of peak $S'$ wave velocity is significantly higher among patients with preserved LV ejection fraction (40) and reduced myocardial contractility when LV function was assessed in vivo in sheep fetuses by end-systolic elastance using a conductance catheter during acidosis induced by placental embolization (26).

We observed that the waveform of myocardial lengthening velocity during isovolumic relaxation (IVRV) could be consistently recorded by pulsed TDI (Fig. 1). This velocity has not been previously described in the literature. During fetal acidosis, we found that the peak IIVRV and the slope of isovolumic myocardial deceleration are reduced. Additionally, a reduction in $E'$ wave velocity (an index of active ventricular relaxation) was noted, but no significant change in the $A'$ wave velocity was observed. These findings suggest that metabolic acidosis can adversely affect the calcium- and energy-dependent active myocardial relaxation during the isovolumic phase and the early phase of diastole, but the ventricular expansion during atrial contraction is not significantly affected; i.e., the atrial contractility is preserved. This is consistent with the finding that, in coronary artery disease, $A'$ wave velocity is significantly higher among patients with preserved LV ejection fraction (>50%) than in those with impaired ejection fraction (44). A change in the cardiac after-

### Table 3. TDI parameters of fetal right ventricle at the level of the tricuspid valve annulus

<table>
<thead>
<tr>
<th></th>
<th>$S'$, cm/s</th>
<th>$E'$, cm/s</th>
<th>$A'$, cm/s</th>
<th>IVCV, cm/s</th>
<th>IVRV, cm/s</th>
<th>Accel, cm/s$^2$</th>
<th>Decel, cm/s$^2$</th>
<th>IVRT, %</th>
<th>IVCT, %</th>
<th>ET, %</th>
<th>Tei Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9.5 ± 2.0</td>
<td>7.1 ± 1.0</td>
<td>11.2 ± 3.0</td>
<td>5.5 ± 1.7</td>
<td>4.0 ± 0.8</td>
<td>596 ± 170</td>
<td>335 ± 74</td>
<td>5.48 ± 1.09</td>
<td>14.2 ± 5.7</td>
<td>7.6 ± 3.1</td>
<td>38 ± 6.6</td>
</tr>
<tr>
<td>Acidosis</td>
<td>8.5 ± 2.3</td>
<td>5.7 ± 1.4</td>
<td>11.5 ± 2.4</td>
<td>4.1 ± 1.5</td>
<td>2.9 ± 0.7</td>
<td>290 ± 106</td>
<td>206 ± 61</td>
<td>7.07 ± 1.41</td>
<td>15.9 ± 2.6</td>
<td>10.3 ± 3.6</td>
<td>38 ± 6.0</td>
</tr>
<tr>
<td>$P$</td>
<td>0.173</td>
<td>0.008</td>
<td>0.728</td>
<td>0.013</td>
<td>0.003</td>
<td>&lt;0.0001</td>
<td>0.026</td>
<td>0.427</td>
<td>0.050</td>
<td>0.967</td>
<td>0.138</td>
</tr>
</tbody>
</table>

Values are means ± SD.

### Table 4. TDI parameters at the septal annulus

<table>
<thead>
<tr>
<th></th>
<th>$S'$, cm/s</th>
<th>$E'$, cm/s</th>
<th>$A'$, cm/s</th>
<th>IVCV, cm/s</th>
<th>IVRV, cm/s</th>
<th>Accel, cm/s$^2$</th>
<th>Decel, cm/s$^2$</th>
<th>IVRT, %</th>
<th>IVCT, %</th>
<th>ET, %</th>
<th>Tei Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.1 ± 2.4</td>
<td>5.2 ± 1.0</td>
<td>8.5 ± 2.4</td>
<td>4.8 ± 1.4</td>
<td>4.0 ± 1.1</td>
<td>523 ± 170</td>
<td>372 ± 128</td>
<td>12.1 ± 4.8</td>
<td>7.4 ± 2.6</td>
<td>37 ± 6.5</td>
<td>0.54 ± 0.13</td>
</tr>
<tr>
<td>Acidosis</td>
<td>6.3 ± 1.0</td>
<td>4.2 ± 1.9</td>
<td>8.4 ± 2.2</td>
<td>3.5 ± 1.3</td>
<td>2.8 ± 0.6</td>
<td>284 ± 88</td>
<td>259 ± 71</td>
<td>11.9 ± 2.4</td>
<td>9.9 ± 3.8</td>
<td>38 ± 4.8</td>
<td>0.57 ± 0.11</td>
</tr>
<tr>
<td>$P$</td>
<td>0.031</td>
<td>0.120</td>
<td>0.714</td>
<td>0.003</td>
<td>0.003</td>
<td>0.002</td>
<td>0.019</td>
<td>0.856</td>
<td>0.033</td>
<td>0.401</td>
<td>0.458</td>
</tr>
</tbody>
</table>

Values are means ± SD.
load can affect indexes describing myocardial relaxation and diastolic properties (25). However, IVRT%, which is known to be affected by changes in loading conditions, remained stable during metabolic acidosis, suggesting that our findings merely reflected the effects of metabolic acidosis. Glucose and lactate account for the majority of myocardial oxygen consumption in sheep fetuses (5), and significant metabolic acidosis leads to depletion of myocardial glycogen and ATP stores, which is reflected the effects of metabolic acidosis. Glucose and lactate account for the majority of myocardial oxygen consumption in sheep fetuses (5), and significant metabolic acidosis leads to depletion of myocardial glycogen and ATP stores, which is associated with impaired repolarization, as evidenced by T wave changes in the fetal electrocardiogram (18). Therefore, inasmuch as disturbances in diastole often precede and may occur independent of changes in global systolic performance, diastolic function assessment can be useful in monitoring fetuses at risk for cardiac dysfunction.

The relatively high TDI Tei indexes in our fetuses at baseline may be explained by increased $R_{ba}$ and higher afterload following placental embolization. The TDI Tei index is shown to correlate with the Tei index obtained by pulsed-wave Doppler and M-mode echocardiography (9) but is affected by loading conditions (7). A previous study in human fetuses with heart failure (2) suggested that the TDI Tei index maybe a sensitive parameter in the assessment of RV function.

We observed no significant changes in fetal ventricular cardiac outputs or ventricular TDI Tei indexes during the experiments. In the absence of altered BPs, abnormal relaxation causes longer IVRT and an increase in Tei index values. However, inasmuch as the fetal aortic pressure and CVP during acidosis were not significantly different from baseline values in our study, it is unlikely that the elevated atrial pressure has masked a detectable rise in the Tei index during acidosis. This suggests that the global cardiac function is relatively well preserved during acute metabolic acidosis, consistent with studies in which the sheep fetuses maintained their cardiac output during hypoxemia (28) and acidosis (26). Human fetuses with clear evidence of placental insufficiency (absent or reversed umbilical artery diastolic blood flow) are also shown to have normal weight-indexed combined cardiac output (24). Even fetuses with increased serum troponin-T levels seem to have normal ventricular shortening fraction and ejection force and appear to maintain their cardiac output (29). This explains why signs of fetal congestive heart failure in intrauterine growth restriction tend to occur late in the disease process and subtle fetal cardiac dysfunction is difficult to detect using conventional echocardiography. Therefore, TDI of fetal myocardial motion could improve the early detection of impending heart failure.

E/E’ of both ventricles was increased during fetal metabolic acidosis. In adults, mitral valve E/E’ has been shown to reflect LV filling pressure (31, 33). In the present study, fetal CVP remained unchanged, suggesting that ventricular filling pressures did not change significantly. Thus an increase in E/E’ was merely reflecting a depression in E’ wave velocity during metabolic acidosis. E/E’ of the LV correlated significantly with the severity of fetal acidosis. We propose that the fetal LV is more sensitive to the changes in oxygenation and acid-base status than the RV. In addition, despite the parallel arrangement of the fetal circulation, the afterload impedance faced by the RV may be different from that faced by the LV during fetal acidosis. In these experiments, the presence of fetal ductal constriction was excluded by serial Doppler studies, but a relative increase in vascular impedances, including the pulmonary vascular bed, could have occurred.

Myocardial velocities recorded by TDI during a cardiac cycle reflect shortening and lengthening of long-axis fibers situated predominantly in the subendocardium. In human fetuses, higher myocardial wall velocities in the RV than LV and IVS have been attributed to segmental differences in myocardial fiber orientation (11, 32). Although there are known

![Image](http://alphanew.ajpheart.physiology.org/Downloadedfromhttp://alphanew.ajpheart.physiology.org/)

### Table 5. Correlations between TDI parameters and fetal pH values

<table>
<thead>
<tr>
<th></th>
<th>Pearson’s $r$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVCV</td>
<td>0.54</td>
<td>0.01</td>
</tr>
<tr>
<td>Accel</td>
<td>0.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IVRV</td>
<td>0.58</td>
<td>0.005</td>
</tr>
<tr>
<td>Decel</td>
<td>0.61</td>
<td>0.003</td>
</tr>
<tr>
<td>Tei index</td>
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<td>0.002</td>
</tr>
<tr>
<td>E/E’</td>
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<td>0.005</td>
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<tr>
<td><strong>Right ventricle</strong></td>
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<td></td>
</tr>
<tr>
<td>IVCV</td>
<td>0.54</td>
<td>0.01</td>
</tr>
<tr>
<td>Accel</td>
<td>0.69</td>
<td>&lt;0.0001</td>
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<tr>
<td>IVRV</td>
<td>0.39</td>
<td>0.074</td>
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<tr>
<td>E/E’</td>
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<td>0.065</td>
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<tr>
<td><strong>Interventric septum</strong></td>
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<tr>
<td>IVCV</td>
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<td>0.002</td>
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<tr>
<td>Accel</td>
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<td>0.004</td>
</tr>
<tr>
<td>IVRV</td>
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<td>0.04</td>
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<tr>
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<td>0.008</td>
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<tr>
<td>Tei index</td>
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structural differences between the ventricles with regard to myocardial fiber orientation and other morphometric parameters in sheep fetuses (39), the myocardial velocities obtained from the RV and LV were not significantly different in our study, suggesting that the amplitudes of myocardial deformation during the cardiac cycle are likely to reflect function, rather than pure anatomy, at least in the presence of increased \( R_{aa} \).

The remarkable ability of fetuses to withstand hypoxia has been attributed to enhanced glycolysis in the myocardium (10, 30). Sheep fetuses maintain their cardiac output following placental embolization, despite a significant reduction in \( Q_{ca} \) (1) and moderate acidosis (26). Therefore, it is not surprising that the global myocardial function assessed by TDI also appeared to be robust in these fetuses, despite significant metabolic acidosis. This can be explained by the ability of the fetal myocardium to extract oxygen maximally from the coronary blood flow, which is probably aided by enhanced oxygen unloading at the tissue level.

**Limitations of the study.** The fetuses in this study were examined under general anesthesia, and there may be some effects of isoflurane on the fetal myocardium. Additionally, species differences must be considered when the results of any animal study are applied to humans. Annuar myocardial velocities may vary with the position of the sample volume and insonation angle. However, care was taken to place the sample volume accurately at the level of the atrioventricular valve annuli, and the angle of insonation was <15° in all cases during repeated measurements. We specifically avoided analyzing TDI velocities offline from two-dimensional acquired data sets because of the inherent limitation of measuring maximal myocardial velocities at relatively low frame rates. Myocardial velocities increase with gestational age (8, 11, 32), and fetal responses to acute hypoxia are known to vary according to gestational age (20). Inasmuch as the same fetus served as its own control, the effect of gestational age was not important for the purpose of our study. However, because we chose to use late-gestation sheep fetuses with a narrow gestational age range for our experiments, we cannot conclude that similar myocardial responses would be seen in younger fetuses.

In the present study, myocardial shortening and lengthening velocities were only measured in the longitudinal direction. Cardiomyocytes in the RV are predominantly arranged longitudinally. The LV has more obliquely and circumferentially arranged myocytes than the RV (13). In adults, LV longitudinal and oblique fibers contract first, followed by circumferential fibers (4), and ventricular long-axis shortening velocities and amplitude correlate with overall ventricular function as assessed by ejection fraction (14). In addition, studies on adults have shown that, in disease states, long-axis shortening tends to decline earlier than radial function (16). In human fetuses, intraobserver variability of TDI measurements has been shown to be comparable to pulsed Doppler-derived parameters (11).

**Conclusion.** In sheep fetuses with increased \( R_{aa} \) and acute metabolic acidosis, the global cardiac function is preserved. Acute fetal metabolic acidosis is associated with impaired myocardial contractility during the isovolumic phase and impaired relaxation during isovolumic and early filling phases of the cardiac cycle.

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**GRANTS.**

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**REFERENCES.**