Preexisting hypoxia is associated with a delayed but more sustained rise in T/QRS ratio during prolonged umbilical cord occlusion in near-term fetal sheep

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Submitted 27 May 2007; accepted in final form 19 July 2007

Wibbens B, Bennet L, Westgate JA, De Haan HH, Wassink G, Gunn AJ. Preexisting hypoxia is associated with a delayed but more sustained rise in T/QRS ratio during prolonged umbilical cord occlusion in near-term fetal sheep. Am J Physiol Regul Integr Comp Physiol 293: R1287–R1293, 2007. First published July 25, 2007; doi:10.1152/ajpregu.00373.2007.— There is limited information about whether preexisting fetal hypoxia alters hemodynamic responses and changes in T/QRS ratio and ST waveform shape during subsequent severe asphyxia. Chronically instrumented near-term sheep fetuses (124 ± 1 days) were identified as either normoxic PaO2 > 17 mmHg (n = 9) or hypoxic PaO2 ≤ 17 mmHg (n = 5); then they received complete occlusion of the umbilical cord for 15 min. Umbilical cord occlusion led to sustained bradycardia, severe acidosis, and transient hypertension followed by profound hypotension in both groups. Preexisting hypoxia did not affect changes in mean arterial blood pressure but was associated with a more rapid initial fall in femoral blood flow and vascular conductance and with transiently higher fetal heart rate at 2 min and from 9 to 11 min of occlusion compared with previously normoxic fetuses. Occulsion was associated with a significant but transient rise in T/QRS ratio; preexisting hypoxia was associated with a significant delay in this rise (maxima 3.7 ± 0.4 vs. 6.2 ± 0.5 min), but a slower rate of fall. There was a similar elevation in troponin-T levels 6 h after occlusion in the two groups [median (range) 0.43 (0.08, 1.32) vs. 0.55 (0.16, 2.32) µg/l, not significant]. In conclusion, mild preexisting hypoxia in normally grown singleton fetal sheep is associated with more rapid centralization of circulation after umbilical cord occlusion and delayed elevation of the ST waveform and slower fall, suggesting that chronic hypoxia alters myocardial dynamics during asphyxia.

ANTENATAL HYPOXIA IS ASSOCIATED with an increased incidence of stillbirth and metabolic acidosis (30, 38) and, in the long term, with abnormal neurodevelopment (38). It is thus important to identify compromised infants as early as possible in labor. The presence of elevation of the ST segment of the fetal ECG, typically measured relative to the QRS complex (the T/QRS ratio), is a marker for the development of fetal metabolic acidosis in clinical and experimental studies (1, 2, 19, 35, 43). The relationship between ST segment changes and fetal compromise is complex (40); however, there is some evidence that preexisting hypoxia can enhance the rise in T/QRS ratio and affect ST waveform shape during subsequent insults (39, 45).

Further, chronic fetal compromise can either improve or impair some fetal responses to subsequent acute insults. For example, chronically hypoxic fetal sheep exposed to acute hypoxia exhibited more pronounced centralization of circulation (6), with enhanced femoral vasoconstriction associated with greater increases in plasma norepinephrine and vasopressin (12). In contrast, when hypoxic twin or triplet fetuses were exposed to repeated umbilical cord occlusion, they developed severe hypotension and metabolic acidosis much more rapidly (44). It is highly likely that these differences reflect the observation that fetal compromise is not a single entity; it may be relatively pure fetal hypoxia, or varying degrees of substrate limitation or acidosis (12). The effect of preexisting hypoxia on responses to prolonged intervals of severe hypoxia is unknown.

We have previously reported that prolonged asphyxia induced by umbilical cord occlusion in near-term fetal sheep is associated with a transient rise in the T/QRS ratio in parallel with initial hypotension, followed by a fall in T/QRS and profound hypotension (44). In the present study, we examined the effect of preexisting, spontaneous fetal hypoxemia on hemodynamic and T/QRS responses to this insult in singleton fetal sheep (29). Troponin T levels were measured to evaluate whether preexisting hypoxia increased fetal myocardial injury after occlusion.

MATERIAL AND METHODS

Surgery. Romney/Suffolk fetal sheep were instrumented between 119 and 126 days gestation (term = 147 days) under general anesthesia (2% halothane in O2) using sterile techniques as previously described in detail (13, 21, 40). All procedures were approved by the Animal Ethics Committee of the University of Auckland. Catheters were placed in the right femoral artery and vein, left and right brachial artery, and the amniotic sac. Ultrasound blood flow probes (size 3S; Transonic Systems, Ithaca, NY) were placed around the left femoral artery, and the right carotid artery for measurement of femoral blood flow (FBF) and carotid artery blood flow (CaBF). ECG electrodes were placed subcutaneously over the right shoulder and chest at apex level to record the fetal ECG. An inflatable silicone occluder was placed around the umbilical cord of all fetuses (In Vivo Metric, Healdsburg, CA). All leads were exteriorized through the maternal flank, and a maternal long saphenous vein was catheterized to provide...
access for postoperative care and euthanasia. The maternal skin incision was infiltrated with a local analgesic, 10 ml 0.5% bupivacaine plus epinephrine (AstraZeneca, Auckland, NZ). Postoperatively, fetal catheters were maintained patent by continuous infusion of heparinized saline (20 U/ml at 0.2 ml/h), and the maternal catheter was maintained by daily flushing.

Recordings. Fetal mean arterial blood pressure (MAP, Novatrans II, MX860; Medex, Hilliard, OH), corrected by subtraction of amniotic pressure, FBF, CaBF, and ECG were recorded continuously. The blood pressure signal was collected at 64 Hz and low-pass filtered at 30 Hz. The fetal ECG was analog filtered between 0.05 and 80 Hz and digitized at 512 Hz. All data were stored to disk using custom software (Labview for Windows, National Instruments, Austin, TX) for off-line analysis.

Experimental procedures. Experiments were conducted 4 to 5 days after surgery, and recordings were begun 24 h before experiments. Fetuses were assigned to either the normoxia group (N, n = 9) if their baseline PaO2 was >17 mmHg or the preexisting hypoxia group (H, n = 5) if PaO2 < 17 mmHg (10, 25), on the day of the study. Fetal asphyxia was induced by rapid inflation of the umbilical occluder with sterile saline of a defined volume known to completely inflate the occluder. Occlusion was confirmed by observation of an immediate sharp rise in MAP and a fall in fetal heart rate (FHR). On completion of the occlusion period, the occluder was deflated over 10 to 15 s to prevent excessively rapid changes in the circulating blood volume. When bradycardia persisted for more than 30 s or fetal blood pressure did not increase to over 25 mmHg in the first 60 s after release of occlusion, then a dose of 0.3 ml of epinephrine (0.1 ml/kg estimated weight) of 1:10,000 epinephrine was given by slow intravenous push.

Fetal arterial blood samples (0.3 ml) were taken 60 min before occlusion, after 2 and 12 min of occlusion, then 30 min, 1, 2, 3, 4, and 6 h after release of the occluder for pH, blood gas, base excess (BE), hematocrit (Hct), and hemoglobin (Hb) determination (845 blood gas analyzer and cooximeter; Ciba-Corning Diagnostics, East Walpole, MA) and for glucose and lactate measurements (model 2300; Yellow Springs Instruments, Yellow Springs, OH). Plasma samples (0.5 ml) were frozen at −80°C for later measurement of cardiac troponin T values using the Elecsys 2010 immunoassay system (Roche-Boehringer, Mannheim, Germany). The adult normal values for our laboratory are <0.03 μg/l and there is a 10% coefficient of variation above this value (26). On completion of the experiment, the ewes and fetuses were killed by an overdose of pentobarbital sodium (9 g iv to the ewe: Pentobarb 300, Chemstrock International, Christchurch, New Zealand).

Data analysis and statistics. Off-line physiological data analysis was performed using Labview-based customized programs (National Instruments). One-minute and 5-s averages of FHR, MAP, FBF, and CaBF were calculated for each fetus. Femoral and carotid vascular conductance (FVC and CVC, respectively) were calculated by dividing mean blood flow by MAP. Conductance was calculated instead of the reciprocal, vascular resistance, because during umbilical cord occlusion the denominator of resistance, blood flow, approaches zero, leading to highly nonlinear, nonparametric changes. In contrast, conductance changes much more linearly, allowing parametric statistics to be used (23). The 5-s average data were used to assess changes in hemodynamic variables in the first 3 min between groups; 1-min average data were used to compare all other changes. The ECG waveform was averaged with respect to the S wave over 5-s intervals.

For each averaged waveform, the ratio between the T height, measured from the level of the PQ interval and the QRS amplitude, was calculated (T/QRS ratio) (44). The raw ECG data for each averaged waveform were visually assessed (B. Wibbens), after coding of the files by a staff member not involved in the experimental study, to identify ST waveform shape changes and to verify software identification of the T-wave.

The effects of occlusion on time sequence data were evaluated by two-way ANOVA with time treated as a repeated measure (SPSS v10, SPSS, Chicago, IL). The baseline period was taken as the mean of the hour before occlusion. Where an effect of group or an interaction between group and time were observed, intergroup comparisons for selected data were performed by one-way ANOVA. Baseline, survival data, and troponin T data were compared by Mann-Whitney U-test. Statistical significance was accepted when P < 0.05. Data are presented as means ± SE or median (range).

RESULTS

We have previously reported FHR, MAP, FBF, T/QRS ratio, and blood gas and acid-base changes in the normoxic group (44). There were no differences between groups in mean gestational age at surgery or fetal weight at post mortem (Table 1). The preexisting hypoxia group showed significantly lower baseline PaO2 and higher Hb, but no significant difference in baseline oxygen content, or pH, PaCO2, BE, lactate, and glucose (Table 2). PaO2 values were also significantly higher in the normoxia group 48 and 24 h before occlusion (22.3 ± 1.1 and 21.5 ± 0.9 mmHg, respectively) than in the preexisting hypoxia group (14.7 ± 1.8 and 14.0 ± 1.4 mmHg, respectively; P < 0.05).

Changes in fetal blood gases, glucose, and lactate. Umbilical cord occlusion was associated with a profound metabolic acidemia, hypoxemia, and hypercarbia in both groups (Table 2). 7/9 normoxic and 2/5 hypoxic animals received epinephrine intravenously for fetal resuscitation after release of occlusion. Six normoxic fetuses and three hypoxic fetuses survived to 6 h after occlusion.

There was no significant difference between groups for PaO2, or for oxygen content during occlusion. Fetal Hb concentrations were significantly higher in the preexisting hypoxia group at 12 min of occlusion. Similarly, Hct tended to be higher overall in the preexisting hypoxia group and was significantly higher than in the normoxic group at 12 min of occlusion (P < 0.05, data not shown). Shortly after occlusion, both groups showed a continuing, similar metabolic acidosis, with a mild but persistent hypercarbia (Table 2); the preexisting hypoxia group had significantly lower values for PaO2 and higher hemoglobin concentrations and hematocrit.

Fetal heart rate and mean arterial blood pressure. Occlusion elicited a rapid fall in FHR in both groups, with no significant difference between groups in the rate or depth of this initial fall (Fig. 1). This was followed by a brief relative increase in FHR in both groups, maximal ~90 to 120 s after occlusion, which was significantly greater in the preexisting

Table 1. Fetal parameters for normoxia and preexisting hypoxia groups

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Weight, g</th>
<th>Gestation, days</th>
<th>Survival, hr</th>
<th>Sex (female: male)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoxia</td>
<td>9</td>
<td>3,349.3 ± 184.2</td>
<td>124.4 ± 0.4</td>
<td>12 (0, 72)</td>
<td>6:3</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>5</td>
<td>3,244.4 ± 184.1</td>
<td>123.0 ± 0.8</td>
<td>16 (1, 72)</td>
<td>2:3</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE or median (range).

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Table 2. Fetal acid-base balance, blood gases, and serum glucose and lactate levels before, during, and after 15 min of umbilical cord occlusion

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>2 min</th>
<th>12 min</th>
<th>30 min post</th>
<th>1 hr post</th>
</tr>
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<tr>
<td></td>
<td>pH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>7.36±0.01</td>
<td>7.22±0.017</td>
<td>6.93±0.01</td>
<td>7.2±0.02</td>
<td>7.25±0.07</td>
</tr>
<tr>
<td>H</td>
<td>7.35±0.02</td>
<td>7.20±0.02</td>
<td>6.97±0.02</td>
<td>7.21±0.02</td>
<td>7.16±0.06</td>
</tr>
<tr>
<td></td>
<td>PaO₂, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>44.7±1.9</td>
<td>69.9±3.7</td>
<td>116.7±0.0</td>
<td>48.5±2.3</td>
<td>49.0±3.5</td>
</tr>
<tr>
<td>H</td>
<td>49.6±3.4</td>
<td>75.7±4.1</td>
<td>111.2±5.8</td>
<td>54.7±3.5</td>
<td>58.0±3.4</td>
</tr>
<tr>
<td></td>
<td>PaO₂, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>21.6±1.1</td>
<td>5.9±0.9</td>
<td>8.8±0.6</td>
<td>26.3±1.3</td>
<td>22.6±2.7</td>
</tr>
<tr>
<td>H</td>
<td>13.6±1.3†</td>
<td>3.8±0.79</td>
<td>8.4±1.2</td>
<td>19.4±2.5*</td>
<td>14.9±1.9*</td>
</tr>
<tr>
<td></td>
<td>BE, mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>-0.3±1.0</td>
<td>-0.8±0.79</td>
<td>-9.8±0.7</td>
<td>-8.8±1.5</td>
<td>-8.9±2.6</td>
</tr>
<tr>
<td>H</td>
<td>2.2±1.9</td>
<td>-1.1±1.1</td>
<td>-8.8±0.3</td>
<td>-6.6±1.0</td>
<td>-8.3±2.8</td>
</tr>
<tr>
<td></td>
<td>Lactate, mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>0.7±0.1</td>
<td>2.0±0.2</td>
<td>5.6±0.2</td>
<td>5.2±0.3</td>
<td>5.9±0.9</td>
</tr>
<tr>
<td>H</td>
<td>1.7±0.4</td>
<td>3.4±0.6</td>
<td>6.2±0.4</td>
<td>5.4±0.3</td>
<td>6.9±0.9</td>
</tr>
<tr>
<td></td>
<td>Glucose, mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>0.6±0.0</td>
<td>0.3±0.0</td>
<td>1.1±0.1</td>
<td>1.6±0.2</td>
<td>1.3±0.2</td>
</tr>
<tr>
<td>H</td>
<td>0.7±0.1</td>
<td>0.3±0.1</td>
<td>0.9±0.2</td>
<td>1.3±0.2</td>
<td>1.1±0.2</td>
</tr>
<tr>
<td></td>
<td>Hb, g/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>10.0±0.5</td>
<td>11.1±0.5</td>
<td>11.1±0.5</td>
<td>10.6±0.4</td>
<td>10.0±0.3</td>
</tr>
<tr>
<td>H</td>
<td>11.8±0.5*</td>
<td>13.2±2.4</td>
<td>13.2±1.8*</td>
<td>14.2±1.0†</td>
<td>13.2±1.0†</td>
</tr>
<tr>
<td></td>
<td>CaBF, mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3.4±0.3</td>
<td>0.5±0.0</td>
<td>0.5±0.0</td>
<td>4.0±0.1</td>
<td>3.2±0.5</td>
</tr>
<tr>
<td>H</td>
<td>3.3±0.9</td>
<td>0.4±0.0</td>
<td>0.6±0.2</td>
<td>3.6±0.5</td>
<td>2.0±0.2*</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. N, normoxic; H, preexisting hypoxia; BE, base excess; Hb, hemoglobin. Blood samples were taken during occlusion at 2 and 12 min. *P < 0.05. †P < 0.01.

hypoxia group (N: 115.4 ± 5.5 vs. H: 163 ± 19.8 bpm, P < 0.05, ANOVA). From ~5 to 7 min onward, all fetuses showed a steady fall in FHR to a nadir at the end of occlusion [not significant (NS) between groups, Fig. 1]. The hypoxic group showed a transiently higher FHR from 9 to 11 min of occlusion than the normoxic group (P < 0.05, ANOVA).

There was no significant difference in baseline MAP or changes during umbilical cord occlusion between groups. In both groups, there was an initial rise in MAP after the start of occlusion to a maxima after 1.9 ± 0.1 vs. 2.1 ± 0.2 min (N vs. H, NS). MAP then progressively fell reaching baseline values after 6.8 ± 0.2 vs. 6.6 ± 0.5 min (NS), with no significant difference in the nadir of MAP at the end of occlusion (9.3 ± 1.0 vs. 11.1 ± 1.1 mmHg, NS). After release of occlusion, the preexisting hypoxia group showed a significantly greater transient increase in MAP compared with the normoxic group from 5 to 12 min after release of occlusion.

**Femoral blood flow and vascular conductance.** Occlusion was associated with a rapid fall in FBF and FVC to a nadir over 1 to 2 min in both groups (Fig. 2). This fall was significantly more rapid in the preexisting hypoxia group, but of similar ultimate magnitude. From the 4th min of occlusion onward, fetal FVC increased over the remainder of occlusion, although it remained significantly lower than baseline values, with no significant difference between groups. This was associated with a brief proportionate increase in FBF that was maximal at 7 min, followed by a progressive fall in association with hypotension. There was no significant difference in changes in FVC or FBF after release of occlusion.

**Carotid blood flow and vascular conductance.** CaBF and CVC were not significantly different between groups during occlusion (Fig. 2). CaBF was maintained around baseline values in all groups for the first 4 min after the start of occlusion and then progressively fell to a nadir at the end of occlusion. CVC fell after the start of occlusion, reaching a nadir at 2 min in both groups, followed by a secondary increase to baseline values at ~9 min, with no further change. CaBF but not CVC was transiently greater in the hypoxia group, from 3 to 6 min after release of occlusion (P < 0.05).

**TQRS and ST segment changes.** The initial T wave orientation was variable but predominantly negative before occlusion. Only one hypoxic animal had a positive baseline T-wave configuration. All fetuses showed a rapid change to a positive T-wave and ST elevation at the onset of occlusion (Fig. 3). The TQRS ratio increased markedly, and peak values of TQRS were reached at 3.7 ± 0.4 min in normoxic fetuses. In contrast, the preexisting hypoxia group showed a significant delay of 3 min before TQRS began to rise, and the peak was reached after 6.2 ± 0.5 min (Fig. 1, P < 0.01). With continued occlusion, the TQRS ratio fell more slowly in the preexisting hypoxia group, such that TQRS values were higher from 8 to 10 min of occlusion, but the groups were not significantly different thereafter. Although a few fetuses in both groups showed brief periods of negative T-waves, the average TQRS ratio remained significantly higher than baseline levels.

The ST waveform shape changes showed a typical sequence of events during baseline, occlusion, and recovery (Fig. 3). With the onset of occlusion, six normoxic animals developed ST elevation (and positive T-waves) (44). Three animals showed a negative ST-segment at the onset of occlusion. All five hypoxic animals showed a positive ST-segment configuration. During continued occlusion, no fetuses developed biphasic waveforms; however, two fetuses in both groups showed ST depression toward the end of occlusion. Two animals in the normoxic group developed heart block; these fetuses did not respond to epinephrine after release of occlusion and died soon after release of occlusion. In the phase of reperfusion, 7 normoxic and 3 hypoxic animals showed biphasic waveforms for 3.5 ± 0.9 and 2.4 ± 0.5 min, respectively (NS).

**Troponin T.** Both groups showed a similar increase in troponin T after the end of occlusion. The normoxic and preexisting hypoxic groups showed an increase from 0.01 (0.01, 0.03) vs. 0.04 (0.02, 0.53) μg/l at baseline, to 0.32 (0.1, 0.82) vs. 0.36 (0.09, 0.82) at 3 h and 0.43 (0.08, 1.32) vs. 0.55 (0.16, 2.32) μg/l at 6 h after release of occlusion (NS between groups, P < 0.001 vs. baseline).
The present study has demonstrated that spontaneous, compensated fetal hypoxia in otherwise well-grown singleton fetal sheep was associated with a significantly delayed, but ultimately more sustained, rise in the fetal ST waveform during prolonged complete umbilical cord occlusion. This change was associated with more rapid initial centralization of blood flow and a slower late fall in fetal heart rate during occlusion. In contrast, preexisting hypoxia did not affect the time course of hypotension or metabolic acidosis during occlusion. Clinically, similar unpredictable acute, catastrophic events, such as abruptio placentae or umbilical cord prolapse remain a significant cause of perinatal morbidity (42). There are conflicting data on how preceding hypoxia affects fetal adaptation to such acute severe, periods of asphyxia (6, 12, 39). The present study examined singleton fetuses with spontaneous hypoxia, but without evidence of other metabolic abnormalities, to avoid confounding the effects of hypoxia with those of limited nutrient supply and growth restriction (12). A limitation of this approach is that we cannot be sure of the precise etiology or timing of the onset of hypoxia, although the partial pressures of oxygen were significantly lower than in the normoxic group for 48 h before the study. Further, there was evidence of compensation by increased hemoglobin levels, allowing similar fetal arterial oxygen contents to the normoxic group despite lower oxygen tensions, which would be consistent with a significant period of hypoxia (11). Given that the fetuses were not significantly different in weight at post mortem and also had normal glucose values, these data suggest a relatively late-onset limitation of placental oxygen exchange.

Dynamic ECG changes have been suggested to reflect anaerobic myocardial metabolism and depletion of myocardial glycogen reserve, augmented by beta-adrenergic stimulation (19, 20). Our previous report showed that the elevation in ST waveform height during severe asphyxia occurs rapidly at a time when blood pressure is markedly elevated (44) and then falls in parallel with the development of progressive hypotension. These data suggest that the ST waveform elevation reflects anaerobic cardiac metabolism, and thus, the subsequent fall in ST waveform height reflects depletion of the major substrate for anaerobic metabolism, cardiac glycogen (19). The
present data demonstrate the first time that preexisting hypoxia was associated with a delayed, but more sustained, rise in ST waveform height. The period of sustained elevation of the ST waveform in the preexisting hypoxia group was associated with a transiently higher fetal heart rate than in normoxic fetuses, suggesting that preexisting hypoxia improved the ability to maintain anaerobic cardiac metabolism.

The mechanism of the delay in the initial rise in ST waveform height in fetuses with preexisting hypoxia is unclear. Limited data, from studies of chronic exposure to high altitude, suggest that hypoxia can be associated with reduced cardiac beta-1 adrenoreceptor responsiveness in fetal sheep, through postreceptor mechanisms (8), which could attenuate fetal ECG changes (19, 20). However, this would not be consistent either with the brief, but markedly greater, increase in fetal heart rate in the preexisting hypoxia group during occlusion, just before T/QRS height began to rise in the present study, or the very similar pattern of changes in arterial blood pressure in the two groups during occlusion. Further, there is evidence as discussed below that sympathetic neural activity is augmented by chronic hypoxia (9, 36). We propose that a combination of changes, including more rapid initial peripheral vasocostriction, and changes in neurotransmitters and intracellular events induced by hypoxia (34) altered cardiomyocyte responses and thus potentially attenuated initial anaerobic stress on the heart (7).

Conceptually, the cardiovascular responses of the fetus to acute severe hypoxia can be considered in two phases, the initial, rapid chemoreflex-mediated adaptations (3, 14), and the subsequent longer period of progressive hypoxic decompensation (4, 27, 28), which cannot be prevented by vagotomy (3). The chemoreflex responses help maintain perfusion to key organs such as the heart, adrenals, and brain, and are believed to reduce myocardial work (10, 27). The present study demonstrated that there was no significant effect of preexisting hypoxia on the initial chemoreflex-mediated bradycardia. However, consistent with previous data (6, 12), the spontaneous hypoxia group showed a significantly faster initial fall in femoral blood flow, mediated by a correspondingly rapid reduction in femoral conductance. These data suggest that the alpha-adrenergic receptor-mediated peripheral arc of the chemoreflex was sensitized by previous hypoxia (14). We may speculate that this helps support fetal adaptation by further reducing myocardial work (10). This effect was specific, as there was no significant difference in the changes in the heart rate responses to the brief, but markedly greater, increase in fetal heart rate in the preexisting hypoxia group during occlusion, just before T/QRS height began to rise in the present study, or the very similar pattern of changes in arterial blood pressure in the two groups during occlusion. Further, there is evidence as discussed below that sympathetic neural activity is augmented by chronic hypoxia (9, 36).

In the present study, the initial peripheral vasocostriction was only sustained for the first 4 min of occlusion in all fetuses and was followed by partial return to baseline values, consistent with previous data in a range of vascular beds during both complete and partial occlusion of the umbilical cord (5, 15, 24, 33, 44). A similar response is also seen after partial occlusion in near-term fetal sheep (15), suggesting that it is not simply an effect of profound hypoxia or acidosis. Loss of peripheral vasocostriction was associated with a further, progressive fall in heart rate, and, after ~6 min, with overt hypotension. There is no evidence for continuing reflex mechanisms at this time (3); likely contributors to impaired cardiac function include hypoxia, acidosis, depletion of myocardial glycogen, and cardiomyocyte injury (17).

Given that peripheral vascular tone never rose above baseline levels, hypotension must have been primarily caused by a fall in combined ventricular output. Because stroke volume is relatively constrained in the fetus (16), cardiac output is a function primarily of the fall in heart rate. Thus the higher fetal heart rate in the preexisting hypoxia group in this phase, from 9 to 11 min of occlusion, suggests better maintenance of cardiac output. Further, the preexisting hypoxia group showed better blood pressure and improved carotid blood flow in the immediate recovery period. Although these data are difficult to interpret in view of the confounding effects of cardiac arrest
and epinephrine (27), the rate of epinephrine administration in the preexisting hypoxia group (40%) tended to be less than in normoxic fetuses (78%). These data indicate the possibility of more robust recovery of cardiac function after asphyxia in fetuses with isolated, well-compensated preexisting hypoxia.

In experimental studies, prior tissue hypoxia or ischemia can improve cardiac recovery under specific circumstances (34). Speculatively, this so called preconditioning may provide a mechanism by which the hypoxic group may have been able to transiently better tolerate asphyxia (34). This may be partly mediated through enhanced adenosine levels (32), which are seen during moderate reductions in oxygen tension comparable with those seen in the preexisting hypoxia group (7). The significant rise in troponin T values after occlusion in the present study was similar in the two groups, suggesting that any difference was related to improved functional recovery rather than reduced myocardial injury per se. Although we cannot rule out a type II error, the preexisting hypoxia group showed a small trend to higher troponin values.

In conclusion, the present data reinforce previous studies, suggesting that elevation of the T/QRS ratio in isolation is a marker for anaerobic cardiac metabolism due to fetal hypoxia rather than for the development of hypotension (41). Moderate preexisting hypoxia in normally grown singleton fetuses was associated with enhanced centralization of circulation after umbilical cord occlusion, a significant delay before elevation of the ST waveform, but a slower subsequent fall and a slower late fall in fetal heart rate after the onset of hypotension, suggesting that preexisting hypoxia can improve myocardial dynamics during subsequent severe asphyxia.

ACKNOWLEDGMENTS

This study was supported by grants from the Health Research Council of New Zealand, Auckland Medical Research Foundation, the Lottery Grants Board of New Zealand, and VSB Fonds and Stichting Nuffic (The Netherlands).

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