Dynamics of cardiovascular responses to repeated partial umbilical cord compression in late-gestation sheep fetus

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1Laboratory for Pregnancy and Newborn Research, Department of Physiology, College of Veterinary Medicine, Cornell University, Ithaca, New York 14853-6401; 2The Physiological Laboratory, University of Cambridge, Cambridge CB2 3EG, United Kingdom; 3Department of Obstetrics and Gynecology, University Hospital Utrecht, 3584 CX Utrecht, The Netherlands; and 4Pregnancy Institute, Slidell, Louisiana 70461

Giussani, Dino A., Nobuya Unno, Susan L. Jenkins, Richard A. Wentworth, Jan B. Derks, Jason H. Collins, and Peter W. Nathanielsz. Dynamics of cardiovascular responses to repeated partial umbilical cord compression in late-gestation sheep fetus. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2351–H2360, 1997.—We characterized the detailed hemodynamics of fetal blood pressure, heart rate, common umbilical blood flow, and femoral blood flow responses to partial compression of the umbilical cord and tested the hypothesis that repeated cord compression modulates fetal cardiovascular responses in 10 chronically instrumented fetal sheep at ~130 days of gestation. In five fetuses (group I), partial compression of the umbilical cord was induced 12 times, each for 5 min at 15-min intervals. Each cord compression reduced common umbilical blood flow by 50% and produced modest falls in fetal pH (7.33 ± 0.0 to 7.29 ± 0) and arterial PO2 (21.1 ± 0.2 to 16.8 ± 0.2 mmHg) and a mild increase in arterial PCO2 (49.9 ± 0.5 to 54.9 ± 0.4 mmHg). Sham experiments were performed in five other fetuses (group II). Second-by-second analysis of group I fetal cardiovascular data revealed a clear biphasic response to partial cord compression. Phase I (1st min of cord compression) was characterized by a rapid bradycardia and a rapid femoral vasoconstriction (primary response); phase II (minutes 2–5 of cord compression) was characterized by a delayed bradycardia and a return of femoral vascular resistance toward baseline (secondary response). Repeated cord compression abolished the primary, but not the secondary, cardiovascular responses. These results demonstrate that fetal cardiovascular responses to stress may be modified by preexposure to repeated intrauterine challenges.

cord occlusion; biphasic response; hypoxia; mechanoreflex

IT IS WIDELY ACCEPTED that the developing fetus may successfully adapt to a single acute hypoxic insult during pregnancy or at birth, but little is known about the effects of repeated hypoxemia on fetal cardiovascular adaptive mechanisms. This is particularly important because clinical evidence suggests that recurrent antenatal hypoxemia will predispose the fetus to subsequent neurodevelopmental handicap, inferred from both neuropathological changes in animal models (6, 19) and from neurodevelopmental follow-up studies in humans (12, 20, 29). Recurrent fetal hypoxemia may thus modify the fetal cardiovascular defense and the mechanisms mediating it, and these changes may persist through to extrauterine life.

Recurrent intrauterine hypoxemia may result from repeated compression of the umbilical cord, leading to an increase in fetal arterial PCO2 (Paco2) and a fall in pH, in addition to fetal hypoxemia (13, 14, 27, 30). Since the first description by Barcroft in 1947 (2), numerous reports in the literature in several species have addressed changes in fetal heart rate patterns and in fetal blood pressure to a single complete or near-complete umbilical cord occlusion or to gradual occlusion of the umbilical cord (1, 13, 14, 16, 17). However, to date few data are available for 1) the effects of controlled partial compression of the umbilical cord on continuous changes in fetal regional circulation, in addition to changes in fetal heart rate and fetal arterial blood pressure, 2) the effects of repeated umbilical cord compression on fetal cardiovascular responses, and 3) the mechanisms mediating fetal cardiovascular responses to cord compression.

Giussani et al. previously demonstrated (10) that the first line of insight to mechanisms mediating control of any specific fetal cardiovascular response to a challenge is to determine in detail the rate of onset of the response. In this study we have paid particular attention to the dynamics of fetal cardiovascular responses to repeated controlled cord compression by analyzing the cardiovascular data second by second. The precise extent of cord compression was quantified by continuous measurement of common umbilical blood flow.

The specific aims of this study in the chronically instrumented late-gestation sheep fetus were thus 1) to characterize continuous changes in fetal arterial blood pressure, fetal heart rate, and femoral hemodynamics to controlled partial compression of the umbilical cord and 2) to test the hypothesis that repeated compression of the umbilical cord will modify the magnitude and gain of these fetal cardiovascular responses. Some of our results were previously published in abstract form (11).

METHODS

Surgical Preparation

Ten pregnant Rambouillet-Colombia ewes, mated on a single occasion and carrying fetuses of known gestational ages, were prepared surgically at 125.2 ± 0.4 (mean ± SE) days of gestation (term normally occurring at 147 days) under general anesthesia (pretreated with 1 mg glycyrpyrrolate im, induced with 1 g ketamine im, and maintained with 1–2% halothane in O2), as previously described in detail (10, 22). In brief, after a midline laparotomy the fetal head was exteriorized for insertion of carotid artery and jugular vein catheters (ID 0.4 mm, OD 0.7 mm) with the tips of the catheters in the...
ascending aorta and superior vena cava, respectively. Another catheter was placed in the amniotic cavity for recording of the reference pressure, and the uterine incision was closed by layers. A second uterotomy was used to exteriorize the fetal hindlimbs for placement of a catheter in the descending aorta, via insertion into the left femoral artery, and implantation of a blood flow transducer (25 or 3S Transit-time flow transducer, Transonic, Ithaca, NY) around the right femoral artery (10). We and others (7, 9, 25) previously reported that continuous measurement of fetal femoral blood flow provides a useful continuous index of blood flow distribution to the peripheral circulations.

After an incision on the fetal left flank, the common umbilical artery was exposed retroperitoneally and another Transonic flow transducer (4R/S or 6R/S) was implanted around it (30). An inflatable cord occluder (OC20HD, In Vivo Metric, Healdsburg, CA) was placed around the proximal end of the umbilical cord and secured onto the fetal abdominal wall so as to avoid contact with the cord when not inflated. After implantation of the common umbilical artery flow transducer, common umbilical blood flow was monitored continuously intraoperatively to prevent compression of the umbilical cord and for fetal health surveillance during placement of the inflatable cord occluder. The second uterine and abdominal incisions were closed, and the catheters and flow probe leads were exteriorized through a maternal flank. Polyvinyl catheters (ID 0.4 mm, OD 0.7 mm) were also inserted into the maternal carotid artery and jugular vein and advanced into the arch of the aorta and superior vena cava, respectively.

All animals were allowed at least 5 days of postoperative recovery before experiments commenced, during which time antibiotics were administered daily to the ewe (1 g ampicillin iv) and into the amniotic cavity (500 mg ampicillin). Anesthesia was provided to the mother for the first 2 days after surgery (phenylbutazone, 0.5 g × 2 po). Vascular catheters were maintained patent by slow, continuous infusion of heparinized saline (25 IU heparin/ml at 0.5 ml/h). All procedures employed were approved by the Cornell University Animal Use and Care Committee and performed in facilities approved by the American Association for the Accreditation of Laboratory Animal Care.

Experimental Procedure

The animals were divided randomly into two experimental groups. In five animals at 130.8 ± 1.9 days of gestation (group I), partial compression of the umbilical cord via inflation of the occluder with sterile saline was induced 12 times, each lasting 5 min with a 15-min interval. Each umbilical cord compression was designed to reduce common umbilical blood flow by 50% of predetermined baseline (see Fig. 1). Fetal carotid blood samples (0.3 ml) were drawn anaerobically into heparinized syringes 1 min before and at the end of each compression period, before cuff deflation, for measurement of arterial blood gases and pH (ABL 500, Radiometer, Copenhagen, measurements corrected to 39.5°C). Fetal carotid blood samples before and after the 1st, 6th, and 12th compressions of the umbilical cord were also analyzed for lactate concentrations. Blood lactate concentrations were determined using 1-lactate oxidase-incorporated membranes together with a platinum electrode for hydrogen peroxide detection (model 2300 Stat, Yellow Spring Instruments, OH). In addition, maternal and fetal arterial blood samples (5 ml) were drawn simultaneously from the carotid catheters before and after the 1st, 6th, and 12th umbilical cord compressions for measurement of plasma adrenocorticotropic hormone and cortisol concentrations (30). Fetal red blood cells from centrifuged tubes were resuspended in sterile heparinized saline (25 IU heparin/ml) and returned aseptically into the fetal arterial circulation. Fetal hemoglobin concentrations by the end of the experimental protocol were within normal baseline ranges (data not shown). Five other fetuses (group II, sham) were submitted to a similar experimental protocol at 130.7 ± 1.6 days of gestation, but the implanted cord occluder was not inflated. All animals underwent necropsy 3 days after the end of the occlusion protocol. At necropsy, fetal body weight in group I and group II animals was 3.6 ± 0.2 and 3.8 ± 0.2 kg, respectively.

Data Collection and Calculations

Calibrated fetal femoral arterial blood pressure, fetal heart rate, and common umbilical artery and fetal femoral artery blood flows were recorded continuously throughout the study using a data acquisition system. Detailed analysis of the fetal cardiovascular variables required data to be collected at 1-s intervals throughout the experimental protocol. Fetal arterial blood pressure was corrected for amniotic pressure. Changes in fetal femoral vascular resistance were calculated by dividing mean fetal arterial blood pressure by mean fetal femoral blood flow (10).

Statistical Analyses

Data were analyzed first by the summary of measures method (21) to focus the statistical comparisons. Mean fetal arterial blood gases, pH, acid/base excess, and lactate were compared before and during cord compression for group I and II fetuses using two-way analysis of variance (ANOVA) followed by the Student-Newman-Keuls test (see Tables 1 and 2).

Second-by-second analyses of the fetal cardiovascular variables revealed a biphasic response to partial compression of the umbilical cord. Summary of measures analysis revealed phase I of the fetal cardiovascular response to last for −1 min and phase II to be minutes 2–5 of the response in group I fetuses. The 5-min average before compression of the cord was taken as baseline for fetal arterial blood pressure, fetal heart rate, fetal femoral blood flow and femoral vascular resistance. For each cardiovascular variable, the maximum or minimum change from baseline (depending on the nature of the response) during the first minute of cord compression was taken as the phase I value. Similarly, the maximum or minimum change from baseline during minutes 2–5 was taken as the phase II value. Absolute maximum or minimum values in fetal arterial blood pressure, fetal heart rate, fetal femoral blood flow and femoral vascular resistance were then assessed during phases I and II between groups for the 1st, 6th, and 12th umbilical cord compression periods using two-way ANOVA followed by the Student-Newman-Keuls test (see Table 3).

Finally, to assess whether cardiovascular responses during phase I (1st min) of the cord compression period became modified after repeated cord compression in group I fetuses relative to group II, the changes from baseline in mean fetal arterial blood pressure, mean fetal heart rate, and mean fetal femoral blood flow during phase I (1st min of cord compression) were compared between the 1st, 6th, and 12th umbilical cord compressions for groups I and II using two-way ANOVA followed by the Student-Newman-Keuls test (see Fig. 4). For all statistical analyses, significance was accepted when $P < 0.05$. 


and a mild reduction in arterial P O2 (PaO2). These changes were not accompanied by significant deviations (1.3 ± 0.1 meq/l) and lactate concentrations (1.6 ± 0.2 mmol/l) during the experimental protocol. During the 12 periods of cord compression the mean falls in pHa and PaO2 were from 7.32 ± 0.01 to 7.29 ± 0.01 and from 21.2 ± 0.2 to 16.9 ± 0.2 mmHg, respectively (± SE), and the mean increase in PaCO2 was from 49.9 ± 0.5 to 54.9 ± 0.4 mmHg. The minimum pHa measured during any compression period was 7.27 ± 0.01. In contrast, fetal pHa, PaCO2, and PaO2 (Table 2) in addition to fetal acid/base excess (−0.1 ± 1.1 meq/l) and lactate concentrations (1.3 ± 0.1 mmol/l) remained unchanged from baseline during the corresponding cord compression periods in group II fetuses.

Table 2. Fetal blood gases and pH during repeated sham umbilical cord compression in group II

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Compression</th>
<th>Postcompression</th>
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<tbody>
<tr>
<td>Time</td>
<td>Before</td>
<td>During</td>
</tr>
<tr>
<td>10 min</td>
<td>7.36 ± 0.00</td>
<td>50.0 ± 1.6</td>
</tr>
<tr>
<td>1 min</td>
<td>7.35 ± 0.01</td>
<td>50.0 ± 1.3</td>
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<tr>
<td>5 min</td>
<td>7.34 ± 0.01</td>
<td>52.6 ± 2.0*</td>
</tr>
<tr>
<td>10 min</td>
<td>7.40 ± 0.01</td>
<td>50.4 ± 0.8</td>
</tr>
<tr>
<td>15 min</td>
<td>7.41 ± 0.01</td>
<td>48.2 ± 1.0</td>
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<tr>
<td>1 h</td>
<td>7.33 ± 0.01</td>
<td>48.2 ± 1.0</td>
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<tr>
<td>2 h</td>
<td>7.32 ± 0.01</td>
<td>48.9 ± 1.0</td>
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<tr>
<td>15 min</td>
<td>7.31 ± 0.01</td>
<td>48.9 ± 1.0</td>
</tr>
<tr>
<td>1 h</td>
<td>7.32 ± 0.01</td>
<td>49.7 ± 0.8</td>
</tr>
<tr>
<td>2 h</td>
<td>7.33 ± 0.01</td>
<td>49.7 ± 0.8</td>
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</tbody>
</table>

Values are means ± SE of baseline (10 min before cord compression protocol), before (−1 min) and during (+5 min) each umbilical cord compression, and at postcompression (15 min, 1 h, and 2 h after compression protocol). pHa, arterial pH; PaCO2, arterial PCO2; PaO2, arterial PO2. *Significant differences (P < 0.05) compared to corresponding value in group II fetuses (Table 2), 2-way analysis of variance (ANOVA) + Student-Newman-Keuls test.

RESULTS

Blood Gas Status

Fetal arterial blood gases and arterial pH (pHa) during the experimental protocol are shown in Table 1 for group I fetuses and in Table 2 for group II fetuses. In group I fetuses, each umbilical cord compression produced modest falls in pHa, modest increases in PaCO2, and a mild reduction in arterial PO2 (PaO2). These changes were not accompanied by significant deviations from baseline in fetal acid/base excess (1.7 ± 0.6 meq/l) or in fetal lactate concentrations (1.6 ± 0.2 mmol/l) during the experimental protocol. During the 12 periods of cord compression the mean falls in pHa and PaO2 were from 7.32 ± 0.01 to 7.29 ± 0.01 and from 21.2 ± 0.2 to 16.9 ± 0.2 mmHg, respectively (± SE), and the mean increase in PaCO2 was from 49.9 ± 0.5 to 54.9 ± 0.4 mmHg. The minimum pHa measured during any compression period was 7.27 ± 0.01. In contrast, fetal pHa, PaCO2, and PaO2 (Table 2) in addition to fetal acid/base excess (−0.1 ± 1.1 meq/l) and lactate concentrations (1.3 ± 0.1 mmol/l) remained unchanged from baseline during the corresponding cord compression periods in group II fetuses.

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<th>Postcompression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Before</td>
<td>During</td>
</tr>
<tr>
<td>10 min</td>
<td>7.35 ± 0.01</td>
<td>46.5 ± 1.4</td>
</tr>
<tr>
<td>1 min</td>
<td>7.35 ± 0.01</td>
<td>48.8 ± 1.3</td>
</tr>
<tr>
<td>5 min</td>
<td>7.35 ± 0.01</td>
<td>47.8 ± 0.9</td>
</tr>
<tr>
<td>10 min</td>
<td>7.34 ± 0.01</td>
<td>47.2 ± 1.6</td>
</tr>
<tr>
<td>15 min</td>
<td>7.34 ± 0.01</td>
<td>47.0 ± 1.0</td>
</tr>
<tr>
<td>1 h</td>
<td>7.33 ± 0.01</td>
<td>47.1 ± 1.0</td>
</tr>
<tr>
<td>2 h</td>
<td>7.32 ± 0.01</td>
<td>47.1 ± 1.0</td>
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</tbody>
</table>

Values are means ± SE of baseline (10 min before compression protocol), before (−1 min) and during (+5 min) each umbilical cord compression, and at postcompression (15 min, 1 h, and 2 h after compression protocol).
Cardiovascular Data

Common umbilical blood flow. Baseline common umbilical blood flows were 157 ± 23 ml·min⁻¹·kg⁻¹ in group I fetuses and 163 ± 28 ml·min⁻¹·kg⁻¹ in group II fetuses when standardized to fetal body weight determined at necropsy. A similar fall in common umbilical blood flow occurred during each of the 12 umbilical cord compressions in group I fetuses (Fig. 1). The mean fall in common umbilical blood flow calculated over the 12 periods of cord compression was 48.8 ± 0.4% of baseline (P < 0.05). In contrast, common umbilical blood flow did not change from baseline in group II fetuses throughout the experimental protocol (Fig. 1).

Dynamics of fetal cardiovascular responses to partial cord compression. Second-by-second analysis of changes in cardiovascular variables revealed a biphasic cardiovascular response during the first umbilical cord compression (Fig. 2). Phase I (1st min of cord compression) was characterized by an abrupt, early fall in fetal heart rate and a rapid increase in fetal femoral vascular resistance (primary cardiovascular responses, Table 3, Fig. 2). During phase II (minutes 2–5 of cord compression), a delayed fetal deceleration occurred and fetal femoral vascular resistance returned towards baseline (secondary cardiovascular responses), despite the continued reduction in common umbilical blood flow (Table 3, Fig. 2).

Modulation of cardiovascular responses by repeated cord compression. In group I fetuses, after repeated partial compression of the umbilical cord the primary fetal bradycardia and fetal femoral vasoconstriction were significantly attenuated at the 6th and 12th umbilical cord compressions, despite similar reductions in common umbilical blood flow (Table 3, Fig. 3A). In contrast, delayed fetal bradycardia persisted past the 6th compression of the umbilical cord and was evident by the 12th cord compression period (Table 3, Fig. 3A).

When the change from baseline in mean fetal arterial blood pressure, mean fetal heart rate, and mean fetal femoral blood flow during phase I (1st min of cord compression) of the cardiovascular responses to the 1st, 6th, and 12th umbilical cord compression was calculated, it was clear that the primary fetal bradycardia and fetal femoral vasoconstriction became significantly attenuated despite similar changes in fetal arterial blood pressure by the 12th cord compression (Fig. 4).

It was of interest to learn whether the attenuation of the fetal primary cardiovascular responses occurred gradually after repeated cord compression or whether these responses were only evident in the first cord compression and became significantly attenuated even by the second cord compression period. Figure 5 demonstrates the fetal heart rate changes for all 12 compressions of the umbilical cord for group I fetuses. It is clear that the primary bradycardia is not just a phenomenon of the first compression of the umbilical cord but that it appeared to become progressively attenuated after repeated compression of the umbilical cord. Notwithstanding biological variation in cardiovascular variables, the changes in mean fetal heart rate, mean common umbilical blood flow, and mean fetal femoral vascular resistance measured in group I fetuses did not
occur in group II fetuses during the experimental protocol (Table 3, Fig. 3B).

**DISCUSSION**

Studies of neuropathological changes in animal models (6, 19) or of neurodevelopmental follow-up in humans (12, 20, 29) demonstrated that intermittent or transient umbilical cord compromise plays a causal role in antenatal central nervous system injury, impaired neurological development, and hippocampal damage. Despite this finding, there is, surprisingly, no knowledge of the effects of repeated cord compression on fetal cardiovascular adaptation. This is the first study to report that repeated compression of the umbilical cord alters the magnitude of fetal cardiovascular responses.

**Fetal Cardiovascular Hemodynamics During Partial Cord Compression**

Second-by-second analyses of the fetal cardiovascular responses to partial compression of the umbilical cord revealed a clear biphasic fetal cardiovascular response. Phase I (1st min of cord compression) was characterized by a rapid early fetal bradycardia associated with fetal femoral vasoconstriction (primary cardiovascular responses). In terms of the fetal heart response, the origin of the bradycardia could be attributed to chemo-, mechano- or baroreflex stimulation. However, because fetal arterial blood pressure did not change significantly during cord compression in this study, it is unlikely that the bradycardia is mediated by a baroreflex. Furthermore, simultaneous changes in the fetal femoral circulation suggest that the primary fetal heart rate response is chemoreflex in origin, because previous experiments in fetal sheep and extrapolation from experiments in adult animals demonstrate that 1) both baro- (15) and mechanoreflex (24, 26) stimulation promote peripheral vasodilatation, not vasoconstriction, but 2) fetal bradycardia and femoral vasoconstriction during hypoxemia are established ca-

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**Table 3. Statistical analyses of fetal cardiovascular responses for group I and group II fetuses during repeated cord compression**

<table>
<thead>
<tr>
<th>Compression</th>
<th>FBP, mmHg</th>
<th>FHR, beats/min</th>
<th>FBF, ml/min</th>
<th>FVR, mmHg·min·ml⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
<td>Group I</td>
<td>Group II</td>
</tr>
<tr>
<td>Baseline</td>
<td>52.1 ± 2.4</td>
<td>48.0 ± 0.9</td>
<td>187 ± 7</td>
<td>175 ± 4</td>
</tr>
<tr>
<td>Phase I</td>
<td>61.4 ± 3.9</td>
<td>53.2 ± 1.8</td>
<td>114 ± 13*</td>
<td>159 ± 5</td>
</tr>
<tr>
<td>Phase II</td>
<td>45.5 ± 1.8</td>
<td>45.1 ± 0.4</td>
<td>116 ± 10*</td>
<td>154 ± 3</td>
</tr>
<tr>
<td>Baseline</td>
<td>51.0 ± 2.6</td>
<td>47.9 ± 1.2</td>
<td>187 ± 7</td>
<td>175 ± 4</td>
</tr>
<tr>
<td>Phase I</td>
<td>59.3 ± 2.3</td>
<td>50.9 ± 1.0</td>
<td>150 ± 6</td>
<td>151 ± 9</td>
</tr>
<tr>
<td>Phase II</td>
<td>47.9 ± 2.5</td>
<td>42.4 ± 1.0</td>
<td>123 ± 13*</td>
<td>158 ± 8</td>
</tr>
<tr>
<td>Baseline</td>
<td>53.0 ± 2.3</td>
<td>47.6 ± 1.3</td>
<td>186 ± 6</td>
<td>175 ± 4</td>
</tr>
<tr>
<td>Phase I</td>
<td>60.3 ± 4.6</td>
<td>52.2 ± 1.9</td>
<td>155 ± 12</td>
<td>166 ± 6</td>
</tr>
<tr>
<td>Phase II</td>
<td>45.9 ± 1.9</td>
<td>44.5 ± 2.2</td>
<td>130 ± 8</td>
<td>145 ± 6</td>
</tr>
</tbody>
</table>

Values are means ± SE for baseline and maximum deviation from baseline during phase I (1st min) and phase II (minutes 2–5) for 1st, 6th, and 12th umbilical cord compressions. FABP, mean fetal arterial blood pressure; FHR, fetal heart rate; FBF, mean fetal femoral blood flow; FVR, mean calculated fetal femoral vascular resistance. *Significant differences (P < 0.05) group I vs. group II, 2-way ANOVA + Student-Newman-Keuls test.
rotid chemoreflexes (3, 9, 10) and 3) one fetus from group I in our experiments did not demonstrate any increase in fetal arterial blood pressure, but fetal bradycardia and femoral vasoconstriction persisted during partial umbilical cord compression.

Although the fall in fetal PaO₂ measured during partial cord compression reported in the present study was modest, the careful experiments of Blanco and colleagues (5) demonstrated substantial chemoreceptor fiber discharge to similar reductions in fetal PaO₂ from ~20 to 16 mmHg in late-gestation fetal sheep, either produced by umbilical cord compression or by maternal inhalational hypoxia. Interestingly, Blanco et al. (5) reported that an increase in carotid chemoreceptor fiber discharge occurred much faster after cord compression (after 10–15 s) than after maternal hypoxemia (after 1 min). Carotid chemoreceptor discharge may be potentiated by transient hypoperfusion of the carotid body (see Ref. 32) and/or by hypercapnia (5), both of which occur during partial compression of the umbilical cord.

Point measurements of fetal peripheral blood flow during varying degrees of umbilical cord compression were previously reported by others with the radiolabeled microsphere technique. Although Ball et al. (1) and Iwamoto et al. (17) reported a peripheral vasoconstriction with acute cord constriction in fetal sheep, results that are in keeping with the femoral hemodynamics reported in the present study, Itskovitz et al. (16) reported an increase in carcass blood flow during umbilical cord compression. The reasons for these differences are unclear. It could be argued that measured changes in femoral blood flow reported in the current manuscript are not representative of changes.
in other peripheral circulations. We acknowledge the fact that femoral blood flow is not a complete index of peripheral blood flow distribution. However, good correlation between continuous changes in fetal femoral blood flow measured with Transonic flow transducers and point measurements of fetal carcass blood flow via radiolabeled microspheres have been previously reported, at least in fetuses of other species (8).

Although it is well accepted that umbilical cord compression will produce fetal hypoxemia, it is less well represented that cord compression will also induce a decrease in venous return to the fetal heart and an increase in umbilical arterial vascular resistance. Each of these components of cord compression will stimulate different mechanisms, eliciting different fetal cardiovascular responses. Repeated compression of the umbilical cord may modify each of these mechanisms differentially.

Knowledge of fetal cardiovascular adaptation to a decrease in venous return to the fetal heart has been gained through experiments involving obstruction of the fetal inferior vena cava in sheep. The elegant experiments of Wood and associates (34) demonstrated that fetal vena caval obstruction could also produce fetal bradycardia despite a decrease in fetal arterial blood pressure. In contrast to the fetal cardiovascular responses to acute hypoxemia, the mechanisms mediating fetal bradycardia in response to decreased cardiac preload have not been fully characterized. However, it is suggested that because fetal bradycardia during fetal vena caval obstruction may occur in the absence of fetal hypoxemia (32, 34), chemoreflex-independent mechanisms may mediate, at least in part, the fetal heart rate responses during fetal vena caval obstruction. Wood (32) reported that sinoaortic denervation, a procedure that eliminates the effects of peripheral chemo- and
baroreceptor afferents but does not affect inputs from cardiac sites (see Ref. 33), reduced the degree of fetal bradycardia in response to vena caval obstruction.

Wood (32) therefore favored an arterial chemoreflex mechanism mediating fetal bradycardic responses to vena caval obstruction. However, the data reported by Wood (32) could be reinterpreted to suggest that sinoaortic denervation attenuates, but does not prevent, fetal bradycardia during vena caval obstruction. Any persisting bradycardia during reduced preload in sinoaortic-denervated fetal sheep may thus be mediated by chemoreflex-independent mechanisms. A possible mechanism to explain persisting bradycardia may be cardiac mechanoreceptors. In adult animals the Bezold-Jarisch reflex, promoting bradycardia during reduced preload in sinoaortic-denervated fetal sheep may thus be mediated by chemoreflex-independent mechanisms.

Thus it is clear that mechanisms mediating fetal decelerations during umbilical cord compression must be multifactorial, originating at least from chemo-, mechano-, or baroreflex influences. Itskovitz et al. (14) reported that fetal bradycardia during umbilical cord compression is of chemoreceptor origin and is mediated via vagal afferents, because fetal treatment with atropine attenuated the fall in fetal heart rate during cord compression. However, fetal cardiac responses to mechano- and baroreflex stimulation are also mediated via the vagus; thus conclusions on the afferents cannot be inferred simply from pharmacological blockade to common efferent pathways of the reflex arcs.

Repeated Cord Compression and Fetal Cardiovascular Responses

One previous study in chronically instrumented fetal sheep investigated the effects on fetal cardiovascular responses of five 5- to 10-min successive periods of uncontrolled cord compression to reduce fetal \( P_a \) to 10–12 mmHg. In that study Lewis et al. (18) concluded that repeated fetal hypoxemia did not alter the magnitude of the fetal arterial blood pressure, heart rate, or catecholaminergic responses. However, that study reported only point measurements of fetal blood pressure and heart rate before and after each cord compression, preventing differentiation of detailed hemodynamic components of these cardiovascular responses. We have demonstrated that repeated compression of the umbilical cord to produce a 50% fall in common umbilical blood flow at every compression produces subtle differences that can only be identified by second-by-second analysis. Repeated cord compression abolished the primary, but not the secondary, fetal cardiovascular responses. These findings support the hypothesis that the magnitude and gain of fetal cardiovascular responses to stress may be modified by repeated preexposure to a challenge. This is of paramount clinical importance because if the fetus adapts to a stress early in gestation, it may reach the end of pregnancy with an
unrecognized fetoplacental reserve deficit for a subsequent acute challenge, such as labor.

Differential effects of repeated cord compression on primary and secondary fetal cardiovascular responses, in addition, support the hypothesis that phases I and II of the fetal cardiovascular responses to cord compression are mediated via different mechanisms. In contrast, concomitant attenuation of the primary fetal bradycardia and fetal femoral vasoconstriction after repeated cord compression supports the hypothesis that these responses may be mediated by a similar mechanism.

If the primary fetal cardiovascular responses to partial umbilical cord occlusion are chemoreflex in origin, then results presented in the present study may imply that fetal cardiovascular chemoreflex responses to stress may be attenuated by repeated cord compression or by preexposure to repeated stress. In contrast, if the secondary fetal cardiovascular responses to partial cord compression are stimulated by a decrease in venous return to the fetal heart, teleologically it may seem reasonable to maintain this mechanoreflex-induced bradycardia to every cord compression because cardiac slowing under ventricular underfill has been suggested to allow better diastolic filling and to improve cardiac pumping efficiency (24).

In conclusion, we have demonstrated that detailed hemodynamic analysis of fetal cardiovascular adaptation to partial compression of the umbilical cord reveals a biphasic cardiovascular response. Phase I (1st min of cord compression) is characterized by a fast, early bradycardia concomitant with a rapid femoral vasoconstriction (primary cardiovascular response); phase II (minutes 2–5 of cord compression) is characterized by a delayed fetal bradycardia and a return of fetal femoral vascular resistance toward baseline (secondary cardiovascular response). Repeated compression of the umbilical cord abolishes the primary, but not the secondary, fetal cardiovascular responses. These studies demonstrate for the first time that the magnitude and gain of fetal cardiovascular responses to stress may be modified by preexposure to repeated intrauterine challenges.

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REFERENCES