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Cholinergic and β-adrenergic control of cardiovascular reflex responses to brief repeated asphyxia in term-equivalent fetal sheep

Robert Galinsky,1,2 Christopher A. Lear,1 Kyohei Yamaguchi,1 Guido Wassink,1 Jennifer A. Westgate,1 Laura Bennet,1 and Alistair J. Gunn1

1Department of Physiology, The University of Auckland, Auckland, New Zealand; and 2The Ritchie Centre, Hudson Institute of Medical Research, Victoria, Australia

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Fetal heart rate (FHR) monitoring is widely used to noninvasively and continuously monitor fetal well-being in labor. Although normal FHR recordings are highly reassuring, i.e., the negative predictive value is strong, the positive predictive value for acidosis or other complications is very low (6, 30). The most characteristic changes in FHR during labor are the recurrent rapid falls in FHR associated with uterine contractions known as intrapartum decelerations (29). In some cases, a rapid increase in FHR above baseline can be seen immediately after the deceleration (43). This pattern of FHR deceleration followed by rapid acceleration above baseline is referred to as heart rate overshoot. This overshoot pattern has been described in fetuses that were subsequently depressed at birth (15) or later developed cerebral palsy (39), suggesting that it might have diagnostic utility.

There is little information on the specific mechanisms of overshoot. There is some evidence that FHR overshoot may reflect progressive fetal acidosis and impaired cerebral metabolism (19, 34, 38). However, in fetal sheep, overshoot can occur well before the onset of fetal compromise (43), strongly inferring an autonomic mechanism, such as a combination of asphyxia-induced inhibition of vagal tone and unopposed β-adrenergic stimulation of the myocardium (43). Parasympathetic inhibition of heart rate (14) is mediated through the M2 muscarinic receptors on cardiac pacemaker cells (41). Although the impact of parasympathetic blockade during brief asphyxia is unknown, it is well established that the initial FHR deceleration during brief asphyxia is a chemoreflex and is mediated by parasympathetic efferents, as recently reviewed by Lear et al. (29). Conversely, β1-adrenergic receptor activation is critical to maintain FHR during hypoxia (7, 37); α-adrenergic activity has no direct effect on the fetal heart (37).

Systematic studies in term-equivalent fetal sheep found that during intermittent brief asphyxia induced by umbilical cord occlusion, the precise duration of occlusion was critical to whether overshoot occurred or not (43). We found that 1-min umbilical cord occlusions repeated every 5 min did not trigger FHR overshoot, whereas it occurred at the very start of a series of 2-min occlusions repeated every 5 min (43). We have recently shown that overshoot is not attenuated by sympatheticommy (28). Nevertheless, levels of circulating catecholamines increase very rapidly during brief asphyxia and, thus, increase β-adrenergic activity independent of the neural sympathetic system (13, 24).

In the present study, we first tested the hypothesis that lack of overshoot after 1 min of umbilical cord occlusion was due to continued vagal tone, and, therefore, that infusion of the M2 receptor antagonist atropine to near-term fetal sheep exposed to 1-min occlusions every 5 min (1:5) would unmask FHR overshoot. We then tested whether β-adrenergic blockade with propranolol would prevent or attenuate FHR overshoot after 2-min occlusions repeated every 5 min (2:5) to test the hypo-
esis that the asphyxia-induced increase in circulating catecholamines stimulates FHR overshoot.

METHODS

Surgical procedures. All procedures were approved by the Animal Ethics Committee of the University of Auckland. Twenty-seven Romney/Suffolk sheep (119-126 days gestation; 147 days) were operated on using sterile techniques. Food, but not water, was withdrawn 18 h before surgery. Ewes were given oxytetracycline (20 mg/kg; Phoenix Pharmaceuticals, Auckland, New Zealand) intramuscularly 30 min before surgery for prophylaxis, to reduce the risk of postsurgical infection. General anesthesia was induced by intravenous injection of propofol (5 mg/kg; AstraZeneca, Auckland, New Zealand) and was maintained using 2-3% isoflurane (Medsource, Ashburton, New Zealand) in O₂. During surgery, ewes received an intravenous infusion of isotonic saline (250 ml/h) to maintain fluid balance and the depth of anesthesia; maternal heart rate and respiration were continuously monitored by trained anesthetic staff.

Instrumentation. A paramedian abdominal incision was made, and the fetal head was exposed through a uterine incision. Polyvinyl catheters were inserted in the right and left brachial artery, brachial vein, and amniotic cavity. A pair of electrodes was sewn over the fetal chest to measure the fetal ECG. An inflatable silicone occluder (In Vivo Metric, Healdsburg, CA) was placed loosely around the umbilical cord near its abdominal insertion. All fetal leads were exteriorized through the maternal flank. Antibiotics (gentamycin, 80 mg; Pfizer New Zealand, Auckland, New Zealand) were administered into the amniotic sac before closure of the uterus. A maternal long saphenous vein was catheterized to provide access for postoperative care.

Sheep were housed in separate metabolic cages with access to water and food ad libitum in a temperature-controlled room (16 ± 1°C, humidity 50 ± 10%) with a 12:12-h light-dark cycle. Five days of postoperative recovery was allowed before experiments. During this time, ewes received intravenous antibiotics daily for 4 days (gentamycin; 80 mg and benzylpenicillin sodium; 600 mg; Novartis, Auckland, New Zealand). Fetal catheters were maintained patent by continuous infusion of heparinized saline (20 IU/ml) at a rate of 0.2 ml/h.

Experimental recordings. Fetal mean arterial blood pressure (MAP) and ECG were recorded continuously for offline analysis using custom data acquisition software (LabView for Windows, National Instruments, Austin, TX). The blood pressure signal was recorded with Novatrans III Gold pressure transducers (Medex, Hilliard, OH), corrected for movement by subtraction of amniotic pressure, and collected at 64 Hz and low-pass filtered at 30 Hz. The fetal ECG was analog-filtered between 0.05 and 100 Hz and digitized at 512 Hz and used to derive FHR.

Experimental protocol. Experiments were conducted at 124-130 days gestation, when neural development approximates that of the term human infant (3, 32). Fetuses received an intravenous infusion of the M2 receptor antagonist atropine (n = 7, atropine sulfate; Sigma-Aldrich, Auckland, New Zealand; 4.8 mg bolus followed by 4.8 mg/h over 30 min) or the nonselective β-adrenoceptor antagonist propranolol (n = 8, propranolol hydrochloride, Sigma-Aldrich; 5 mg bolus followed by 5 mg/h over 30 min). Vehicle controls received an equivalent volume of intravenous isotonic saline. Group allocations (treatment vs. vehicle control) and treatment (propranolol vs. atropine) were randomly assigned. Intravenously administered propranolol and atropine both have a half-life of ~2 h (18, 40).

Inusions were started 15 min before occlusions and maintained until the end of the occlusion series. Total umbilical cord occlusions were performed by rapid complete inflation of the occluder with a known volume of saline. Atropine-treated fetuses underwent three 1-min umbilical cord occlusions repeated every 5 min (3 × 1:5) and propranol-treated fetuses underwent three 2-min occlusions repeated every 5 min (3 × 2:5). Vehicle controls received either 3 × 1:5 occlusions (n = 8) or 3 × 2:5 occlusions (n = 6). Fetal arterial blood gas analysis (ABL 800; Radiometer, Copenhagen, Denmark), and measurements of glucose and lactate (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH) were performed immediately before the first occlusion and immediately after the end of the third occlusion. At the end of the experiment, ewes and fetuses were killed by an overdose of pentobarbital sodium (9 g iv to the ewe; Pentobarb 300; Chemstock International, Christchurch, New Zealand).

Data analysis and statistics. To enable accurate assessment of the immediate adaptive phase of the chemoreflex during umbilical cord occlusions, 5-s averages of MAP and FHR were derived for each fetus. The rate of change in MAP and FHR during umbilical cord occlusion was derived by calculating the slope (y) for each of the variables, where y is the difference in pressure or FHR/total duration of the occlusion (min) in the 1:5 groups or the final minute of occlusion in the 2:5 groups. Fetal heart rate overshoot height was defined as the maximum acceleration in FHR immediately after the occlusion (within the first 30 s after release of the occluder) that was 15 beats or more above the baseline FHR before occlusion.

Statistical analyses were undertaken using SPSS (v22, SPSS, Chicago, IL) and Sigmaplot software (v12, SYSTAT, Chicago, IL). Between- and within-group comparisons of fetal blood gases, glucose, lactate, FHR, and MAP were performed by two-way repeated-measures ANOVA. Physiological data for each occlusion and recovery (interocclusion) period were analyzed individually. When statistical significance was found between groups or between group and time, post hoc comparisons were made using a Fisher’s least significant difference test. Mann-Whitney U-tests were used for testing nonparametric data. Statistical significance was accepted when P < 0.05.

RESULTS

Before occlusions. Baseline fetal pH, blood gases, glucose, and lactate concentrations did not differ between groups (Tables 1 and 2). Atropine infusion caused a transient increase in FHR (from 161 ± 6 to 199 ± 8 bpm; P < 0.05) that returned to baseline values before occlusion. Propranolol infusion reduced FHR (from 170 ± 7 to 142 ± 3 bpm; P < 0.05) until occlusions began. Before occlusions, there was no effect of infusion on MAP in the atropine (preinfusion 45 ± 1 vs. postinfusion 46 ± 2 mmHg) or propranolol (preinfusion 43 ± 1 vs. postinfusion 44 ± 2 mmHg) groups.

Table 1. Fetal arterial blood gases and glucose and lactate concentration in control and atropine-treated fetuses exposed to 1-min occlusions every 5 min (1:5)

<table>
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<tr>
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<th>Control</th>
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<tr>
<td>Before</td>
<td>7.41 ± 0.01</td>
<td>7.41 ± 0.01</td>
<td>21.3 ± 0.6</td>
<td>21.6 ± 1.6</td>
<td>45.7 ± 1.0</td>
<td>42.2 ± 1.6</td>
<td>0.9 ± 0.0</td>
<td>0.9 ± 0.0</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>After</td>
<td>7.36 ± 0.01#</td>
<td>7.34 ± 0.02#</td>
<td>17.5 ± 1.1#</td>
<td>16.5 ± 0.8#</td>
<td>48.2 ± 1.7#</td>
<td>47.4 ± 2.2#</td>
<td>1.9 ± 0.4#</td>
<td>1.7 ± 0.9#</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.1</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. #P < 0.05 vs. before occlusion within groups.
Effect of cholinergic blockade on the cardiovascular adaptation during 1:5 occlusions. In the vehicle controls, umbilical cord occlusions were associated with rapid bradycardia and hypertension (Fig. 1, A and B). In atropine-treated fetuses, FHR was markedly higher compared with controls during all three occlusions (Fig. 1A; P < 0.05). In atropine-treated fetuses, a small transient increase in FHR was seen early after the start of the first two occlusions. During the latter stage of the second and third occlusions (within 54 and 50 s from the start of the occlusion, respectively), a small reduction in FHR was observed in atropine-treated fetuses compared with controls (Fig. 2A; P < 0.05). The absolute rate of increase in MAP was higher in the atropine group compared with controls during occlusions (Figs. 1B and 2B; P < 0.05).

Effect of cholinergic blockade on the interocclusion period (1:5 occlusions). During the interocclusion periods, FHR rapidly returned to near-baseline levels, and MAP remained elevated above baseline in controls. In atropine-treated fetuses, FHR and MAP were markedly higher compared with controls (Fig. 1, A and B; P < 0.05). Overshoot tachycardia was not observed in controls; however, all atropine-treated fetuses developed overshoot tachycardia immediately after all three occlusions (Fig. 5; P < 0.05 vs. control).

Fetal arterial blood gases, glucose, and lactate concentrations after 1:5 occlusions. Umbilical cord occlusions were associated with a small fall in pH and PaO₂, and increases in PaCO₂ and lactate that did not differ between groups (Table 1; P > 0.05 vs. before occlusion).

Effect of ß-adrenergic receptor blockade on the cardiovascular adaptation during 2:5 occlusions. In vehicle controls, umbilical cord occlusions were associated with a rapid-onset bradycardia that was sustained for the first minute of occlusion. A small increase in FHR was observed during the second

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Table 2. Fetal arterial blood gases and glucose and lactate concentration in control and propranolol-treated fetuses exposed to 2-min occlusions every 5 min (2:5)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Propranolol</th>
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<tbody>
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<td>pH</td>
<td>7.41 ± 0.01</td>
<td>7.40 ± 0.01</td>
<td>7.34 ± 0.01</td>
<td>7.28 ± 0.01*</td>
<td>7.34 ± 0.01</td>
<td>7.28 ± 0.01</td>
<td>7.34 ± 0.01</td>
<td>7.28 ± 0.01</td>
<td>7.34 ± 0.01</td>
<td>7.28 ± 0.01*</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>22.0 ± 1.0</td>
<td>20.3 ± 1.9</td>
<td>19.7 ± 0.6</td>
<td>19.7 ± 1.2</td>
<td>20.2 ± 2.1</td>
<td>48.1 ± 1.7#</td>
<td>16.0 ± 0.3#</td>
<td>2.6 ± 0.4#</td>
<td>1.0 ± 0.1#</td>
<td>1.1 ± 0.1#</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>46.3 ± 2.0</td>
<td>41.7 ± 1.6</td>
<td>52.2 ± 2.1</td>
<td>48.1 ± 1.7#</td>
<td>52.2 ± 2.1</td>
<td>48.1 ± 1.7#</td>
<td>52.2 ± 2.1</td>
<td>48.1 ± 1.7#</td>
<td>52.2 ± 2.1</td>
<td>48.1 ± 1.7#</td>
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<tr>
<td>Lactate, mmol/l</td>
<td>0.7 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.0</td>
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<tr>
<td>Glucose, mmol/l</td>
<td>46.3 ± 2.0</td>
<td>41.7 ± 1.6</td>
<td>52.2 ± 2.1</td>
<td>48.1 ± 1.7#</td>
<td>52.2 ± 2.1</td>
<td>48.1 ± 1.7#</td>
<td>52.2 ± 2.1</td>
<td>48.1 ± 1.7#</td>
<td>52.2 ± 2.1</td>
<td>48.1 ± 1.7#</td>
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</tbody>
</table>

Data are expressed as means ± SE. *P < 0.05 vs. control; #P < 0.05 vs. before occlusion within groups.

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Fig. 1. Fetal heart rate (FHR; A) and mean arterial pressure (MAP; B) in control (open circles) and atropine-treated fetuses (solid circles) exposed to 3 × 1 min occlusions every 5 min. The shaded region denotes the period of asphyxia. Data are expressed as means ± SE. *P < 0.05 vs. control.

Fig. 2. Rate of change (slope) of FHR (A) and MAP (B) during the first, second, and third umbilical cord occlusion in control (open bars) and atropine-treated fetuses (solid bars) exposed to 3 × 1 min occlusions every 5 min. Data are expressed as means ± SE. *P < 0.05 vs. control.
minute of occlusion (Fig. 3A). In propranolol-treated fetuses, occlusions were associated with a greater reduction in FHR throughout the first and second occlusions (Fig. 3A; \( P < 0.05 \)). In controls, MAP increased rapidly during occlusions (Fig. 3B). In propranolol-treated fetuses, the increase in MAP was attenuated compared with vehicle controls during the first occlusion (\( P < 0.05 \); Fig. 3B). During the second and third occlusions, MAP increased during the first 15 s in the propranolol group and then rapidly fell below the level of controls (\( P < 0.05 \); Fig. 3B). The rate of FHR recovery during the second minute of the first occlusion was reduced in propranolol-treated fetuses compared with controls (\( P < 0.05 \); Fig. 4A); there was no significant difference between groups during the second (\( P = 0.08 \) vs. control) and third occlusions. During the second minute of occlusions, the slope of MAP was lower in propranolol-treated fetuses compared with controls (\( P < 0.05 \); Fig. 4B).

Effect of \( \beta \)-adrenergic receptor blockade on the interocclusion period (2:5 occlusions). After each 2-min occlusion, rapid-onset overshoot tachycardia was consistently observed in controls, followed by progressive resolution to near-baseline levels. In contrast, propranolol infusion was associated with reduced FHR compared with controls (\( P < 0.05 \); Fig. 3A), as well as marked attenuation of overshoot, such that after the first occlusion, FHR recovered to near-baseline levels. After the second and third occlusions, although a small, transient tachycardia occurred in propranolol-treated fetuses, the magnitude of FHR overshoot was substantially reduced compared with controls (\( P < 0.05 \); Fig. 5B). During the interocclusion periods, MAP remained higher in propranolol-treated fetuses than controls (\( P < 0.05 \); Fig. 3B).

Fetal arterial blood gases, glucose and lactate concentrations after 2:5 occlusions. In both groups, 2-min occlusions were associated with reduced pH and increased \( \text{PaCO}_2 \), lactate, and glucose concentrations, relative to baseline values (\( P < 0.05 \)). A greater increase in arterial lactate concentration and a reduction in \( \text{pH} \) were observed in propranolol-treated fetuses compared with controls (\( P < 0.05 \); Table 2).

DISCUSSION

Brief repeated asphyxia lasting 1 or 2 min was associated with a rapid chemoreflex response in intact fetuses, as shown by rapid-onset bradycardia and hypertension.

Occlusion for 1 min did not induce FHR overshoot in controls, consistent with previous observations (43, 44). Cholinergic blockade with atropine nearly completely attenuated the fetal chemoreflex-mediated bradycardia during asphyxia, exaggerated the initial hypertensive response, and unmasked dramatic FHR overshoot after release of occlusion. In contrast, 2-min occlusions were associated with FHR overshoot after
onset bradycardia, we observed a small, progressive fall in partial umbilical cord occlusion (19).

We and others have previously shown that onset bradycardia likely reflects maintenance of myocardial hypoxia than previously suggested. In both groups, MAP increased during 1-min occlusions. However, a greater increase in MAP was observed in atropine-treated fetuses than vehicle controls. Previous studies have shown that increased MAP during brief asphyxia and isocapnic hypoxia is mediated by increased peripheral vascular tone, initially through activation of α-adrenergic efferents, followed by increased circulating vasoactive agents, including catecholamines (13, 14, 22, 25). We did not measure peripheral perfusion in this study; however, it has previously been reported that atropine does not augment peripheral vasoconstriction in near-term fetal sheep during hypoxia (14, 36). Combined ventricular output in the fetus is strongly related to FHR, because stroke volume is constrained (16). Therefore, increased MAP in the atropine group during asphyxia likely reflects maintenance of FHR and combined ventricular output compared with a proportionate reduction in vehicle controls (14).

Interestingly, the difference in MAP between atropine-treated fetuses and controls was attenuated during the second and third occlusions. We and others have previously shown that circulating catecholamines, such as epinephrine and norepinephrine increase exponentially within the first 2 min of umbilical cord occlusion (from 118 ± 20 to 44,495 ± 9,557 and 1,401 ± 236 to 88,937 ± 17,374 pmol/l, respectively) and play a significant role in maintaining MAP during fetal asphyxia (13, 36). Combined ventricular output in the fetus is strongly related to FHR, because stroke volume is constrained (16). Therefore, increased MAP in the atropine group during asphyxia likely reflects maintenance of FHR and combined ventricular output compared with a proportionate reduction in vehicle controls (14).

Cardiovascular adaptation to asphyxia during β-adrenergic blockade. Infusion of the β-adrenergic antagonist propranolol reduced baseline FHR compared with controls, consistent with previous reports (26). During occlusions, a rapid bradycardia was observed in both groups; however, FHR remained lower in propranolol-treated fetuses than controls, presumptively reflecting the negative chronotropic effect of β-adrenergic blockade (9). In controls, partial recovery of FHR was observed during the second minute of occlusion, similar to previous reports (28, 42). This evolving FHR pattern was attenuated in the propranolol group during the first and second occlusions, with a reduced rate of change in FHR during the second minute of occlusion. These data suggest that this considerable increase in circulating catecholamines may have allowed both groups to achieve a similar level of hypertension during subsequent occlusions.

Cardiovascular adaptation to asphyxia during cholinergic blockade. Cholinergic blockade with atropine abolished the chemoreflex-mediated bradycardia and was associated with greater hypertension during 1-min umbilical cord occlusions, as shown by a higher MAP and a greater increase in the rate of rise of MAP in the atropine group than controls. These data confirm a central role of the parasympathetic nervous system in controlling the efferent limb of the chemoreflex during complete umbilical cord occlusion, consistent with previous observations from studies of isocapnic hypoxia (10, 14, 31, 36) and partial umbilical cord occlusion (19).

Although atropine pretreatment prevented the initial rapid-onset bradycardia, we observed a small, progressive fall in FHR during the second and third occlusions. We speculate that this may reflect a cumulative effect of asphyxia on circulating adenosine levels. Adenosine has been shown to be an integral contributor to the bradycardic response during isocapnic hypoxia, as shown by marked attenuation of the reduction in FHR in hypoxic fetal sheep exposed to the adenosine receptor antagonist, 8-(p-sulfophenyl)-theophylline (27). Alternatively, it may reflect a cumulative effect of myocardial hypoxia on cardiac function. Previous observations have shown that 3 min or more of continuous hypoxia is associated with a sustained FHR deceleration that cannot be reversed by atropine (2, 17). Further, vagotomized fetuses show a reduction in FHR after 2-3 min of umbilical cord occlusion (45). The present observation of a small, but significant, reduction in myocardial hypoxia than previously suggested.

During 2-min occlusions, MAP initially increased in both groups, however, propranolol-treated fetuses did not sustain
the increase in MAP. This likely reflects a reduction in combined ventricular output caused by the negative chronotropic and inotropic effects associated with inhibition of myocardial \(\beta\)-adrenergic activity (8).

**Effects of cholinergic and \(\beta\)-adrenergic blockade during the interocclusion period.** In vehicle controls, after 1-min occlusions, FHR rapidly but progressively returned to baseline levels. These data demonstrate that there is no significant loss of vagal tone during a brief episode of asphyxia in the absence of systemic compromise, as previously reported (43). Atropine infusion was associated with FHR overshoot immediately after 1-min occlusions. Strikingly, the magnitude of the overshoot unmasked by atropine was highly similar to that seen after a 2-min occlusion. Although the tachycardia gradually resolved, FHR remained elevated during the interocclusion period compared with controls. These data are consistent with observations in human fetuses during labor (33) and fetal sheep exposed to prolonged isocapnic hypoxia (17), which showed overshoot tachycardia with maternal and fetal atropine treatment, respectively. Collectively, these data indicate that loss of vagal tone is integral to the development of FHR overshoot.

After occlusions, MAP remained increased in atropine-treated fetuses compared with controls. Given that stroke volume is constrained in the fetus (16), the increase in MAP in the atropine group is likely to be a product of the greater increase in FHR compared with controls, in addition to continuing relative peripheral vasoconstriction in both groups, as previously shown (13, 22).

After 2-min occlusions, propranolol treatment markedly attenuated FHR overshoot compared with controls. Furthermore, FHR remained reduced compared with controls in propranolol-treated fetuses throughout the interocclusion period. In chemically sympathectomized near-term fetal sheep, we have previously reported that sympathetic neural activation does not mediate FHR overshoot during brief repeated asphyxia (28). Collectively, these data demonstrate that the increase in circulating catecholamines is essential to enable FHR overshoot, by increasing myocardial \(\beta\)-adrenergic activity.

Mean arterial pressure was increased after occlusions above baseline values in both propranolol-treated fetuses and controls. However, propranolol was associated with a more prolonged increase in MAP. Given that FHR was lower than controls in propranolol-treated fetuses, the prolonged increase in MAP was likely mediated by peripheral vasoconstriction. Supporting this, we observed greater systemic acidosis in the propranolol group compared with controls after occlusions, as shown by a lower arterial pH and higher lactate concentration. This is consistent with previous evidence that acute infusion of propranolol in fetal sheep was associated with mixed respiratory and metabolic acidosis (1). Together, these data suggest that propranolol reduced fetal cardiac output, leading to reduced placental and tissue perfusion.

We speculate that the lower MAP during occlusions reflected impaired centralization of blood flow in the propranolol group, which leads to a greater rise in circulating catecholamines and increased duration of peripheral vasoconstriction after occlusion. Alternatively, it is possible that increased peripheral vasoconstriction in the propranolol group may have been mediated indirectly through blockade of \(\beta_2\)-receptors on blood vessels, leading to unopposed \(\alpha\)-adrenergic mediated vasoconstriction. Further studies are required to resolve this question.

Collectively, these observations demonstrate an integral role of cholinergic and \(\beta\)-adrenergic activity in mediating the chemoreflex response to brief repeated asphyxia at rates and durations consistent with early and active labor. The data strongly confirm that the FHR overshoot pattern that can be observed after asphyxia is mediated by a combination of reduced vagal activation and increased \(\beta\)-adrenergic stimulation of the fetal heart.

**Perspectives and Significance**

The ability of the mammalian fetus to rapidly adapt to an asphyxial insult is crucial to survival. Labor is characterized by intermittent but brief asphyxia during contractions, typically lasting no more than 1 to 2 min. Thus, understanding the physiological controls of adaptation is of fundamental importance. There is compelling evidence that the chemoreflex is central to the initial rapid adaptation. The intrapartum deceleration reduces myocardial work (4, 5, 22), and peripheral vasoconstriction (13, 14, 22) redistributes combined ventricular output to vital organs such as the brain, heart, and adrenals (20, 21, 23). \(\beta\)-Adrenergic antagonists, such as propranolol, are used to treat hypertension in pregnancy, and have been associated with reduced birth weight (35). The present study highlights the critical role of \(\beta\)-adrenergic activation to the cardiovascular adaptation during brief asphyxial episodes that are typical of active labor and supports previous studies in the sheep that \(\beta\)-adrenergic antagonists compromised fetal adaptation to asphyxia (11). These data suggest that \(\beta\)-adrenergic antagonists should be used with caution, if at all, in labor.

Furthermore, there is evidence from studies of brief repeated asphyxia that chemoreflex-mediated sympathetic efferent responses become attenuated after 1 to 2 min of asphyxia, but are reactivated in between the episodes of asphyxia (13, 28). The present study suggests that a similar pattern is observed in the parasympathetic arm of the chemoreflex response, such that vagal activity becomes attenuated after 1 to 2 min of asphyxia but recovers rapidly with reperfusion. Although the evidence is indirect, the point at which vagal inhibition occurs during asphyxia may represent the point in time when myocardial hypoxia contributes to a deceleration. This would reflect the transition from a period of asphyxia that is completely compensated for by the fetus, to one that is not. A marker of this transition may be clinically useful. The present study strongly suggests that this transition is, albeit imperfectly, reflected by the development of overshoot tachycardia immediately after a deceleration. Furthermore, the onset of suppression of vagal activity in the present study is a direct function of the duration of an individual occlusion. Thus, we propose that it may have utility in gaining an understanding of how fetal autonomic adaptation evolves over time.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.
REFERENCES


