Contractile Activity of the Uterus Prior to Labor Alters the Temporal Organization of Spontaneous Motor Activity in the Fetal Sheep

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Contractile activity of the uterus before the onset of labor (uterine contractions) has been described in a number of species and provides a powerful source of repeated stimulation for the fetus throughout much of gestation. To understand how fetal behavior responds to this dynamic aspect of the intrauterine environment, we investigated the effects of uterine contractions on the temporal organization of spontaneous motor activity in the fetal sheep during the last fifth of gestation. Eleven fetuses were instrumented on 113–116 days of gestation (dGA). Electromyogram (EMG) activity was recorded from flexor and extensor muscles in the fetal forelimbs and hindlimbs, and from the uterus. Pooled limb EMG activity from 2300 hr to 0700 hr on 118, 125, 132, and 139 dGA before, during, and after uterine contractions was spectral analyzed to detect and quantify the cyclic organization in fetal motor activity. There was strong evidence of cyclic organization in fetal motor activity (CM) at each gestational age, similar to what has been described in the fetal rat and human. There was no evidence of developmental changes in the baseline spectral measures of CM. The most prominent feature of the response of CM to uterine contractions was a transient decrease in irregularity at 118–132 dGA. The strength of CM increased during contractions at 125 and 132 dGA, and a slight acceleration of CM during contractions was detected at 118 and 139 dGA. The results demonstrate that the stimulation associated with contractures influences an important source of complexity in early behavioral organization. The results are consistent with speculation by others that uterine contractures might induce transient cerebral hypoxemia in the fetus, and suggest that conditions established in the first few minutes of sustained uterine activity constitute the effective perturbation of CM.   © 1996 John Wiley & Sons, Inc.

The intrauterine environment of the mammalian fetus is rich with sensory input, and the effects of this stimulation on fetal behavior and development are now beginning to be understood (e.g., Lecanuet, Fifer, Krasnegor, & Smotherman, 1995). One powerful source of repeated stimulation for the fetus is the contractile activity of the uterus. Regular myometrial activity is present long before labor begins and is a pervasive property of the immediate physical environment experienced by the fetus (Jenkin & Nathanielsz, 1994). In this article we describe the temporal organization of spontaneous motor activity in the fetal sheep, a standard animal model of human fetal physiology, and document the perturbing effects of uterine contractile activity on these patterns of motor organization in the last fifth of gestation.

Prolonged, low-amplitude, coordinated contractions of uterine muscle separated by many minutes of relative quiescence are known to occur throughout much of pregnancy in a number of species, including the sheep (Nathanielsz, Bailey, Poore, Thorburn, & Harding, 1980), rhesus monkey (Taylor, Martin, Nathanielsz, & Seron-Ferre, 1983), baboon (Morgan et al., 1992), and human (Braxton Hicks, 1872). The characteristics of spontaneous uterine activity and its effects on the fetus have been most extensively studied in the sheep in which bursts of coordinated contractile activity can be observed by midgestation (Harding et al., 1982; Thorburn, Harding, Jenkin, Parkington, & Sigger, 1984). Beyond 100 days of gestation in the sheep (term is approximately 145 days), coordinated myometrial activity throughout the uterus lasting 3 or more min and resulting in a 3- to 5-mm Hg rise in intrauterine pressure occurs approximately one to four times per hour (Nathanielsz et al., 1980). These episodes of slow uterine activity separated by many minutes have been called contractures (Nathanielsz et al., 1977) or Type A contractions (Lye, Wlodek, & Challis, 1984) to distinguish them from the brief, high-amplitude contractions recurring at short intervals during labor. Contractures are not triggered by fetal movement (Mulder & Visser, 1987; Nathanielsz, Yu, & Cabalum, 1982). Similar bursts of uterine muscle activity have been recorded in nonpregnant sheep during the estrus cycle (Harding et al., 1982) and in transplanted uterine tissue in pregnant sheep (Thorburn et al., 1984).

Numerous physiological, mechanical, and neuroelectric effects of uterine contractures have been documented in the fetal sheep. During contractures, fetal blood pressure

increases (Brace & Brittingham, 1986; Llanos, Court, Block, Germain, & Parer, 1986; Shields & Brace, 1994), arterial oxygen tension and oxygen content decrease (Hofmeyr, Bamford, Gianopoulos, Parkes, & Dawes, 1985; Jansen et al., 1979; Llanos et al., 1986), and arterial carbon dioxide tension increases (Jansen et al., 1979; Llanos et al., 1986). Based on concurrent measurements of umbilical blood flow, fetal oxygen consumption increases slightly during contractures (Llanos, Block, Court, Germain, & Parer, 1988). Distortion of the fetal thorax has been documented as well (Harding & Poore, 1984; Nathanielsz et al., 1980). Neuroelectric changes in the fetus associated with uterine contractures include a decrease in rapid eye movements and an increase in the amplitude of electrocortical activity (Hofmeyr et al., 1985; Nathanielsz et al., 1980). The incidence of fetal breathing also decreases (Hofmeyr et al., 1985; Nathanielsz et al., 1980).

In contrast to our expanding knowledge of the physiologic, mechanical, and neuro-electric effects of contractures, their effects on the organization of spontaneous fetal motor activity are poorly understood, although a transient increase in body movements during the ascending part of contractures has been observed in near-term human fetuses (Mulder & Visser, 1987). In view of the prenatal emergence of organized behavior patterns and the links between fetal experience and postnatal behavior in numerous species (Lecanuet et al., 1995; Nijhuis, 1992; Smotherman & Robinson, 1988), the possible effects of repeated uterine contractures throughout much of gestation on the organization of spontaneous fetal motor activity are of considerable theoretical and practical interest.

A prominent aspect of motor organization in the embryo and fetus of a wide variety of vertebrate species is *cyclic motility* (CM), consisting of irregular oscillations in spontaneous motor activity on a time scale of minutes or less (Corner, 1977; Hamburger, 1963). Although the functional consequences of this cyclic organization of motor activity for the fetus are unknown, it may play a role in prenatal neuromuscular maturation (Robertson, 1988b). Postnatal CM in the human exhibits transient changes in response to physical and social stimulation (Lalley, 1993; Robertson, 1993b), and appears to regulate fundamental aspects of attention (Robertson & Bacher, 1992; Robertson, Lalley, Bacher, Reilly, & Wood, 1995). These findings raise the possibility that CM might also play an important role in interactions between the fetus and its intrauterine environment (Robertson & Bacher, 1995).

In the human, CM is present by midgestation (Robertson, 1985) and may be related to early burst–pause patterns of motor activation observed in first trimester fetuses (de Vries, Visser, & Prechtl, 1982). Human CM is relatively stable throughout the second half of gestation and is unchanged by birth (Robertson, 1985, 1987). Although maternal diabetes appears to disrupt fetal CM early in the third trimester, it is quantitatively and qualitatively normal by the end of gestation and remains so after birth even in neonates with clinical evidence of exposure to an altered metabolic environment in utero (Robertson, 1988a; Robertson & Dierker, 1986; Robertson, Klugewicz, & Lalley, 1992). Relatively abrupt developmental changes in awake CM occur around 2 months after birth with the increased strength of higher frequency fluctuations in motor activity (Robertson, 1993a). Although it is difficult to study the mechanism responsible for CM directly in humans, brief sound-induced perturbations of CM during active sleep in neonates produce transient changes in CM that are consistent with a single-source model. However, a multisource model (see below) can explain additional patterns in the human data. In either case, preliminary calculations indicate that CM in the human infant may be governed by chaotic dynamics, suggesting that both the persistence and irregularity of oscillations in motor activity may be inherent properties of the same underlying mechanism (Robertson, Cohen, & Mayer-Kress, 1993).

Similar irregular cyclic fluctuations in spontaneous motor activity exist in the fetal rat near the end of gestation (Smotherman, Robinson, & Robertson, 1988), although the dominant cycle times tend to be shorter than in the human. CM is a robust aspect of behavioral organization in the fetal rat, but it is also sensitive to both direct manipulation of the brain's neurochemistry (Simonik, Robinson, & Smotherman, 1994) and to peripheral sensory input from ecologically relevant stimulation (Reilly, Snyder, Mac-Lellan, Robertson, & Smotherman, 1995). Transection of the thoracic spinal cord in the fetal rat does not abolish CM in either rearlimb or nonrearlimb activity; furthermore, CM generated above the transection has a longer cycle time than CM generated below the transection, which is similar to CM in the intact animal (Robertson & Smotherman, 1990a). These findings suggest that the fluctuations in spontaneous motor activity are not controlled by a single source and that if multiple sources exist they may have different preferred frequencies of oscillation.

Preliminary evidence indicates that irregular cyclic fluctuations in spontaneous motor activity, similar to those observed in the fetal human and rat, also exist in the fetal sheep (Robertson & Bacher, 1995). The characteristic temporal patterns were present in electromyographic activity recorded from individual flexor and extensor muscles in the fetal forelimbs and hindlimbs, as well as in the pooled activity of the muscles. In these preliminary data, the rate of oscillation in fetal CM at the end of gestation appeared to increase slightly in response to spontaneous uterine contractures, and there was tentative evidence that CM in the fetal sheep, as in the human, might be governed by chaotic dynamics.

The fetal sheep provides a valuable opportunity to extend our knowledge of how the intrinsic organization of fetal behavior responds to the dynamic aspects of the intrauterine environment. Therefore, the present study was designed to (a) document the existence of CM in the fetal sheep during the last fifth of gestation, (b) provide a quantitative characterization of its spectral properties, and (c) determine the immediate effects of spontaneous uterine contractures on the spectral properties of fetal CM.

Methods

Subjects

The subjects were 11 sheep fetuses from timed matings of 11 Rambouillet-Colombia *(Ovis aries)* ewes. At approximately 100 days of gestational age (dGA), ewes were transferred from the field to the Laboratory for Pregnancy and Newborn Research in the New York State College of Veterinary Medicine at Cornell University and housed in individual metabolism cages (1.25 × 0.50 × 0.85 m) under a 14/10 hr light/dark cycle (lights on at 0700 hr). Ewes were fed alfalfa cubes and water ad libitum for the duration of the study. Ewes and fetuses were cared for according to guidelines established by the New York State College of Veterinary Medicine and the National Institutes of Health (1986). The protocol for this study was approved by the Cornell Institutional Animal Care and Use Committee. All facilities were approved by the American Association for the Accreditation of Laboratory Animal Care.

Instrumentation of Fetuses

Fetuses were instrumented on 113–116 dGA using procedures described previously (Robinson, Wong, Robertson, Nathanielsz, & Smotherman, 1995). Ewes were given a ketamine (1,000 mg) and glycopyrollate (0.12 mg) preanesthetic. Surgery was conducted

with the ewe under 2.0% halothane anesthesia, which also anesthetizes the fetus (Towell, Figueroa, Markowitz, Elias, & Nathanielsz, 1987). Maternal carotid and jugular polyvinyl catheters were placed to permit the prophylactic administration of ampicillin sodium (1,000 mg), an intravenous drip of Ringer's lactate solution, and to obtain blood samples to monitor maternal blood gases.

The fetus was exteriorized through a midline laparotomy and an incision through the uterine wall. When there was more than 1 fetus (one set of twins, three sets of triplets), the largest was instrumented and the remaining fetuses were removed. Polyvinyl catheters were placed in a fetal carotid artery and jugular vein and filled with heparinized saline. Arterial blood samples were obtained to monitor fetal blood gases. Fetal blood pressure and heart rate were monitored by a pressure transducer (Cobe; Arvada, CO) connected to the fetal arterial catheter.

Fetal forelimb flexor and extensor muscles (brachialis, triceps) and hindlimb flexor and extensor muscles (tibialis anterior, gastrocnemius) were instrumented with pairs of electromyogram (EMG) electrodes, sewn 3–5 mm apart, to measure fetal motor activity. An indifferent electrode was sewn into the back of the fetal neck. EMG electrodes were placed on the body and pregnant horn of the uterus to record myometrial activity. All catheters and wires were exteriorized through two sites in the ewe's lateral abdominal wall. A topical antiseptic spray (Blu-kote; Morris, NJ) was applied to all incision sites after closure of the uterus and maternal abdomen.

Following surgery, each ewe received a prophylactic antibiotic regimen consisting of a continuous intravenous infusion of chloramphenicol (2 g/day) for 4 days. Ewes were also given an oral analgesic (Phenyl Gel-4; Butler; Columbus, OH) twice daily for the first 2 days after surgery. Maternal and fetal vascular catheters were continuously infused with sterile heparinized saline (20 units/ml of 0.9 g/liter saline) at a rate of 0.5 ml/hr. Maternal and fetal arterial blood samples (0.5 ml) were obtained daily. Oxygen saturation, hemoglobin, pH, pO_2, and pCO_2 were measured with a Hemoximeter and ABL600 blood gas analyzer (Radiometer; Copenhagen, Denmark) to monitor the condition of the ewe and fetus. At the completion of the study, subjects were euthanized with an overdose of sodium pentobarbital. A postmortem examination was performed on all fetuses to confirm that the catheters and EMG electrodes were still in place.

Data Acquisition

Data acquisition began 5 days after the fetus was instrumented and continued until the end of gestation. EMG signals were processed online using hardware and software components designed specifically for this purpose (Figueroa, Mahan, Poore, & Nathanielsz, 1985). The signals were band-pass filtered (3 to 20 Hz), full-wave rectified, low-pass filtered at 10 Hz, and digitized at 32 Hz with 8 bit resolution. The digitized data were integrated over successive 1-s intervals and the resulting time series were stored for subsequent analysis.

Data Reduction

Data acquired at 118, 125, 132, and 139 dGA (±2 days) were screened for usable contractures (see below). Only data acquired between 2300 and 0700 hr were used in order to minimize the influence of any diurnal variation in fetal and maternal variables and to minimize the influence of environmental disturbances, which are more common during the daylight hours. With four exceptions, data were not used if fetal pH (measured between 0800 and 0900 hr) was less than 7.30. (On three occasions data were used
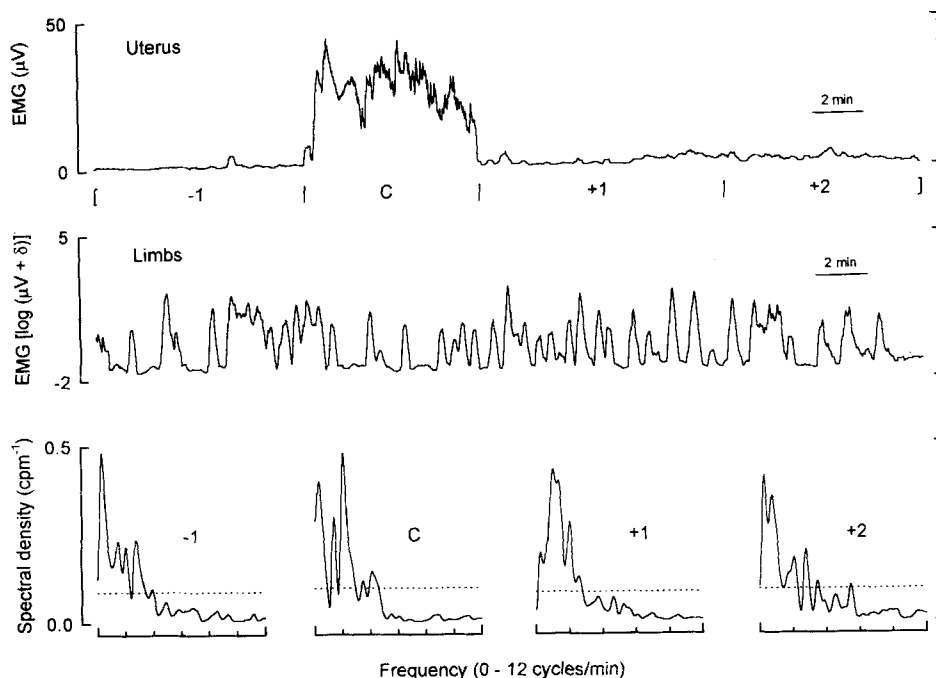
Fig. 1.   Uterine and limb EMG time series in a fetus at 119 days of gestation. (top) Spontaneous uterine contracture (C, 7.1 min), including the periods before (−1, 8.5 min) and two periods after (+1, 10.0 min; +2, 8.0 min) the contracture. (center) Pooled fetal limb EMG time series (unweighted mean) constructed from EMG activity recorded from the left brachialis, triceps, gastrocnemius, and tibialis muscles; δ = .196 μV, the resolution of the analog to digital conversion of the limb EMG signals for this recording (8 bits, full scale = 50 μV). (bottom) Limb EMG spectra for the indicated periods before, during, and after the contracture. The time series in these illustrations were smoothed by computing a 15-s moving average; all spectra were computed from the unsmoothed data. The horizontal dashed line in each spectrum is the upper 99% confidence limit of the spectral estimates for white noise.

when fetal pH was between 7.28 and 7.30, and on one occasion when it was 7.26.) One fetus provided no usable data for the 118 dGA window because it was instrumented too late (at 116 dGA). One fetus died before the 139 dGA window, and labor contractions began before the 132 dGA window in 1 ewe and before the 139 dGA window in 2 ewes.

Contractures were defined as sustained EMG activity recorded from the body of the uterus such that the 15-s moving average remained above baseline for 3 min or more (Figure 1), a definition consistent with those used in previous investigations of spontaneous uterine contractures in the pregnant sheep (Figueroa et al., 1985). A total of 661 contractures were identified using this criterion. So that sufficient time would be available to analyze the effects of contractures on CM, contractures were not used if they were preceded or followed within 5 min by sustained uterine EMG activity (15-s moving average above baseline for 2 min or more, n = 179) or by the beginning or end of the section of data (n = 46). An additional eight contractures were not used for other reasons (EMG artifacts, excessive baseline uterine activity, ambiguous onset or offset), leaving 428 contractures for the analysis of CM. Table 1 contains the number of contractures (total and usable) identified at each gestational age, the duration of the usable contractures, and (for usable contractures) the interval of time between the onset of the contracture and the end of the preceding contracture (usable or not).

Table 1
Total and Usable Contractures

	Days of Gestational Age			
	118	125	132	139
Number of fetuses	10	11	10	7
Total contractures	195	207	170	89
mean (*SD*)	19.5 (7.4)	18.8 (5.7)	17.0 (6.5)	12.7 (4.6)
range	13–35	12–32	9–34	7–20
per hour				
mean (*SD*)	2.0 (0.3)	2.0 (0.6)	2.0 (0.9)	1.6 (0.6)
range	1.6–2.5	0.8–3.3	0.7–4.3	0.9–2.5
Usable contractures	121	136	103	68
mean (*SD*)	12.1 (4.0)	12.4 (7.3)	10.3 (5.0)	9.7 (3.9)
range	6–17	1–27	3–17	5–15
per hour				
mean (*SD*)	1.3 (0.6)	1.3 (0.6)	1.2 (0.6)	1.2 (0.5)
range	0.8–2.1	0.1–2.1	0.4–2.1	0.6–1.9
duration[1] (min)				
mean (*SD*)	6.8 (2.2)	6.3 (1.7)	6.4 (2.4)	6.4 (1.7)
range	3.0–14.8	3.1–11.3	3.0–18.4	3.0–11.2
interval[1,2] (min)				
mean (*SD*)	22.6 (10.3)	26.5 (19.2)	31.6 (27.6)	31.6 (18.8)
range	6.4–64.1	6.0–138.0	5.3–143.5	5.6–109.6

[1] Pooled across fetuses.

[2] Interval of time between the onset of a usable contracture and the end of the preceding contracture (usable or not).

The EMG time series from the fetal forelimbs and hindlimbs were pooled (unweighted mean) to obtain a measure of general motor activation. Prior to pooling, baseline shifts in the EMG time series (due to electrical noise) were removed by subtracting a 15-s moving minimum from the series. Extensive testing indicated that a 15-s window was short enough to remove the baseline shifts but long enough to leave bursts of EMG activity associated with motor activation unaffected. Because the EMG distributions were skewed, the natural logarithm of the pooled EMG time series [$\ln(x + 1)$, $0 \leq x \leq 255$, x = pooled EMG time series] was used in all subsequent analyses.

For each of the 428 usable contractures, the pooled limb EMG time series was divided into segments corresponding to the 10-min period before, the period during (see Table 1), and the 10-min period after the contracture. For reasons described earlier (the presence of other uterine activity or the boundary of a data section), the period before or after some contractures was less than 10 min (83 periods before, mean ± *SD* = 7.44 ± 1.46 min; 68 periods after, 7.46 ± 1.55 min). For 284 contractures there was also a second period after the contracture (87 were less than 10 min, 7.32 ± 1.40 min). Of the 1,568 segments, 15 contained insufficient limb EMG activity to justify subsequent spectral analysis and 3 were contaminated by artifacts (excessive noise in the EMG signals). The remaining 1,550 segments of pooled limb EMG activity were analyzed.

Spectral Analysis of Pooled Limb EMG

The cyclic organization in each segment of the pooled limb EMG time series was analyzed using techniques described in detail in previous reports (e.g., Robertson, 1987) and summarized here. First, each segment was Fourier analyzed, and the cumulative

variance distribution was compared to the theoretical distribution of a white-noise process using a Kolmogorov-Smirnov test (Jenkins & Watts, 1968). A significant departure, $p < .05$, from the theoretical distribution was taken as evidence that the fluctuations in limb EMG activity were not random.

If the fluctuations were nonrandom, the segment was spectral analyzed (after removing any linear trend) to identify and quantify the main components of any cyclic organization. Computational routines provided by Jenkins and Watts (1968) and a Tukey lag window with a bandwidth of 0.50 cycles/min were used to estimate the spectral density function, which provides a measure of the relative strength of cyclic organization at each frequency and thereby permits comparisons between EMG time series in which the total variance may differ due to such factors as changes in electrode contact impedance, muscle maturation, or differences in electrode placement. A spectral peak that exceeded the upper 99% confidence limit of the spectral estimates of a white-noise process (Jenkins & Watts, 1968) was assumed to reflect cyclic organization in fetal motor activity.

For each segment, the two largest peaks in the EMG spectrum that exceeded the upper 99% confidence limit of the spectral estimates of white noise were identified. Three measurements were made on each peak to quantify the properties of the corresponding cyclic components of CM (Robertson, 1987). The frequency of the peak was used to quantify the dominant rate of oscillation of the corresponding component of CM, the height of the peak was used as a measure of the relative strength of the component, and the width of the peak at half-maximum was used as a measure of the irregularity of the component. Because curvilinear trends and slow oscillations (with cycle times on the order of the length of the time series) are difficult to distinguish, the measurements on spectral peaks corresponding to cycle times of 5 min or longer (0.20 cycles/min or less) were not used in subsequent analyses.

Results

Existence of CM

There was strong evidence of cyclic organization in fetal motor activity in all 1,550 segments of pooled limb EMG. For each segment, the cumulative variance distribution based on a Fourier analysis of the EMG time series departed from the theoretical distribution of a white-noise process, $p < .001$ in all segments, and there was at least one peak in the EMG spectrum that exceeded the upper 99% confidence limit of the spectral estimates of a white-noise process. In all but three segments, there was also a second peak at a higher ($n = 1041$) or lower frequency ($n = 506$) that exceeded the upper 99% confidence limit of white noise. The average frequency of the low-frequency peak was 0.78 ± 0.48 cycles/min (mean $\pm$ SD, $n = 1496$ segments), excluding 54 segments (all with at least two peaks) in which the low-frequency peak was located at 0.20 cycles/min or lower, corresponding to a cycle time of 5 min or longer (see Methods). The high-frequency peak was located at 2.01 ± 0.94 cycles/min ($n = 1547$ segments).

Rate, Strength, and Irregularity of CM

For each fetus at each gestational age, the frequency, height, and width of the two largest peaks in the EMG spectra (as described earlier) were averaged separately for the segments before, during, and after the contractures to obtain estimates of the rate,
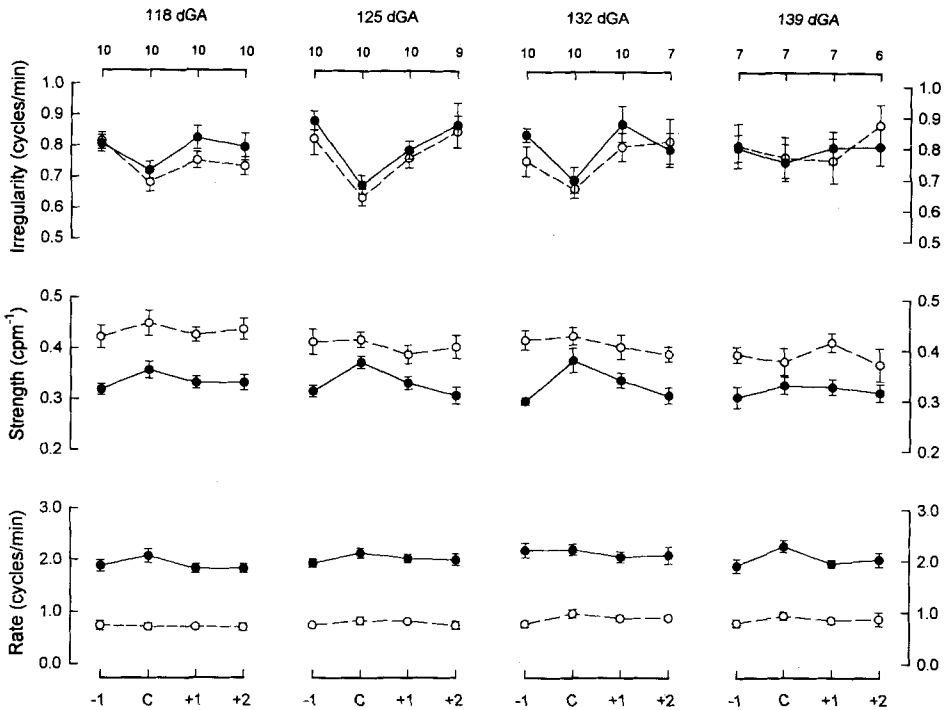
Fig. 2.   Estimates (mean ± *SEM*) of the rate, strength, and irregularity of the low-frequency component (broken line) and high-frequency component (solid line) of CM for the 10-min period before (−1), the period during (C), and the two 10-min periods after (+1, +2) spontaneous uterine contractures at 118, 125, 132, and 139 days of gestation. The number of fetuses contributing data (those with at least three replicates) are shown above the top panel.

strength, and irregularity of the low- and high-frequency components of CM. These spectral measures of CM were used for all subsequent analyses unless otherwise indicated. Results for a segment were not used if there were fewer than three replicates. Group means and standard errors for the spectral measures of CM are shown in Figure 2.

Development of CM

The spectral measures of CM obtained from the segments preceding the contractures (Figure 2) were analyzed using a Component (low, high frequency) × GA (118, 125, 132, 139 dGA) analysis of variance (ANOVA), with repeated measures on both factors. There were no main effects of GA or interactions between component and GA, $ps >$ .4, and thus no evidence for developmental changes in the spectral measures of CM. However, only 5 fetuses had usable data at every GA, which limited the power of this overall analysis.

The spectral measures of CM obtained from the segments preceding the contractures were also analyzed with Component × GA ANOVAs in which pairs of GAs were examined separately using more of the available data. Again, there were no main effects of GA or interactions between component and GA in any of these analyses, $ps >$ .05, and thus no evidence for developmental changes in the spectral measures of CM. Nine fetuses provided usable data for the comparisons among 118, 125, and 132 dGA; 6 or

7 fetuses provided usable data for comparisons with 139 dGA (6 at 118 and 125 dGA, 7 at 132 dGA).

Response of Fetal CM to Uterine Contractures

The effects of spontaneous uterine contractures on CM were analyzed by testing the 2nd order polynomial (quadratic) contrasts over period (before, during, after contracture) in the Period × Component (low, high frequency) ANOVA of each spectral measure at each gestational age.

Evidence that fetal CM was perturbed by uterine contractures was strongest at 125 and 132 dGA (Figure 2). At both gestational ages, the *irregularity of CM decreased,* $F(1,9) = 12.03$, $p = .007$, at 125 dGA; $F(1,9) = 14.53$, $p = .004$, at 132 dGA, and the *strength of CM increased,* $F(1,9) = 8.41$, $p = .018$, at 125 dGA; $F(1,9) = 9.77$, $p = .012$, at 132 dGA, during contractures. The rate of oscillation was unaffected, $ps > .1$. There were no quadratic interactions between period and component, $ps > .1$, and thus no evidence that the low-frequency and high-frequency components of CM responded differently to contractures.

At 118 dGA, the decrease in the irregularity of CM during contractures was less dramatic, $F(1,9) = 6.60$, $p = .030$, and there was no significant increase in the strength of CM, $p > .07$. Again, there were no quadratic interactions between period and component, $ps > .1$, for the irregularity and strength of CM. However, a quadratic interaction between period and component, $F(1,9) = 6.89$, $p = .028$, for the rate of oscillation provided some evidence that CM was influenced by contractures at 118 dGA, although the effects on the low- and high-frequency components were different: The high-frequency component appeared to speed up slightly while the low-frequency component remained unchanged (Figure 2).

By the last week of gestation (139 dGA), spontaneous uterine contractures no longer had any detectable influence on the irregularity or strength of fetal CM, $ps > .06$ (see Figure 2). However, there was a slight increase in the rate of oscillation of CM during contractures, $F(1,6) = 6.22$, $p = .047$, especially in the high-frequency component, as reflected in the quadratic interaction between period and component, $F(1,6) = 6.30$, $p = .046$.

With one exception, CM in the segments *after* contractures did not differ from CM in the segment before the contractures, $ps > .06$. The exception was at 125 dGA, when the decrease in irregularity from baseline persisted into the first 10-min period following the contractures, $F(1,9) = 15.53$, $p = .003$.

There was no evidence that the changes in the spectral measures of fetal CM during contractures were systematically related to the duration or integrated amplitude of the contracture (amplitude of uterine EMG above baseline summed for the duration of the contracture), or to the elapsed time since the end of the preceding contracture. The possibility of such relations was examined at each gestational age in individual subjects with usable data from at least 10 contractures (8 fetuses at 118 dGA, 7 at 125, 5 at 132, and 3 at 139). For each fetus, the linear and quadratic relations between ΔCM (the change in the rate, strength, or irregularity of the low- or high-frequency component of CM from before the contracture to during the contracture) and each of the contracture measures were analyzed. Thus 24 analyses (6 change variables × 4 GAs) were carried out for each of the three contracture measures, with the following results. (a) *Contracture duration:* In 21 of the 24 analyses there was at most 1 fetus that exhibited a significant, $p < .05$, linear or quadratic relation between ΔCM and the duration of the contracture.

In the remaining three analyses, 2 fetuses exhibited a significant liner or quadratic relation, but in each case the relation was qualitatively different in the 2 fetuses; (b) *Integrated amplitude:* In 23 of the 24 analyses there was at most 1 fetus that exhibited a significant relation between ΔCM and the integrated amplitude of the contracture. In the remaining analysis, 3 (of 8) fetuses exhibited a significant relation; only 2 of them were qualitatively similar; (c) *Elapsed time:* In all 24 of the analyses, there was at most 1 fetus that exhibited a significant relation between ΔCM and the elapsed time since the end of the preceding contracture.

There was no evidence that the changes in the spectral measures of fetal CM during contractures were secondary to changes in the average amplitude of the EMG signals recorded from the fetal limb muscles during contractures. The possibility of such a relation was investigated at each gestational age in the same subjects used in the analysis of contracture measures above. For each fetus, the linear and quadratic relations between ΔCM and the change in the average value of the EMG time series were analyzed. For 22 of the 24 analyses (6 change variables $\times$ 4 GAs), there was at most 1 fetus that exhibited a significant, $p < .05$, linear or quadratic relation between the change in CM and the change in EMG. In the remaining two analyses, 2 fetuses exhibited a significant linear or quadratic relation, but in only one of those analyses was the relation qualitatively similar in the 2 fetuses.

Developmental Changes in Response of CM to Contractures

Developmental patterns in the response of fetal CM to uterine contractures were analyzed by testing the interaction between GA and the quadratic trend over period (the response to the contracture), and the dependence of this interaction on component, in the Period (before, during, after contracture) $\times$ GA (118, 125, 132, 139 dGA) $\times$ Component (low, high frequency) ANOVA for each spectral measure. Only 5 fetuses provided usable data at every gestational age, which limited the power of these overall analyses.

The decreased irregularity of CM (in response to contractures) described in the preceding section exhibited a linear trend over GA, $F(1,4) = 14.65, p = .019$, diminishing as gestation progressed. There was some weaker evidence for a curvilinear trend in this response over GA that differed for the low-frequency and high-frequency components of CM, a three-way interaction between component, period (quadratic), and GA (quadratic), $F(1,4) = 7.78$, $p = .049$, reflecting a slightly more pronounced increase in responsiveness at 125–132 dGA in the high-frequency component. There were no significant interactions with GA in the increased rate and strength of oscillation in response to contractures, $ps > 0.1$.

The developmental patterns in the response of fetal CM to uterine contractures were also analyzed with Period $\times$ GA $\times$ Component ANOVAs in which pairs of GAs were examined separately using more of the available data. Nine fetuses provided usable data for the comparisons among 118, 125, and 132 dGA; 6 or 7 fetuses provided usable data for comparisons with 139 dGA (6 at 118 and 125 dGA, 7 at 132 dGA).

The analyses using pairs of GAs revealed two modest interactions between the quadratic trend over period (the response to contractures) and GA. The increased strength of CM in response to contractures diminished from 132 to 139 dGA, $F(1,6) = 6.10, p = .049$, and the increased rate of oscillation in response to contractures became more pronounced between 125 and 139 dGA, $F(1,5) = 11.49, p = .019$.

Discussion

The Ubiquity and Stability of CM

The results provide strong evidence for the pervasive existence of cyclic fluctuations in the spontaneous motor activity of the fetal sheep throughout the last fifth of gestation. Furthermore, the oscillations in pooled EMG activity recorded from forelimb and hind-limb flexor and extensor muscles in the fetal sheep are roughly similar to the oscillations in motor activity in the human fetus measured indirectly by conformational changes in the mother's abdomen (e.g., Robertson, 1985), and similar to the oscillations in motor activity in the exteriorized rat fetus observed directly (e.g., Smotherman et al., 1988). The rate of oscillation for the low-frequency component of CM in the fetal sheep is similar to the dominant rate of oscillation in the fetal rat, both of which are faster than the dominant rate of oscillation in the fetal human. (Separate low- and high-frequency components of CM have not been studied systematically in the fetal rat and human.) The presence of cyclic organization in all 1,550 segments of fetal limb EMG activity analyzed in this study adds further weight to previous claims (Corner, 1977) that irregular oscillation on the scale of seconds to minutes is a fundamental and ubiquitous property of the spontaneous output of the developing vertebrate motor system.

As in the human (Robertson, 1985), quantitative measures of CM in the fetal sheep change very little during the last fifth of gestation. This finding supports the conclusion based on human data that during a period of rapid neurobehavioral development the mechanism responsible for CM has relatively stable dynamic properties. It had been speculated, however, that fetal CM might nevertheless be constantly perturbed on shorter time scales by various intrauterine events (Robertson, 1993b). The results of the present study confirm this speculation. The constancy of CM over developmental time scales in the fetal sheep is in sharp contrast to its sensitivity to uterine contractures on shorter time scales.

It is an open and theoretically important question whether (a) the developmental constancy of CM exists *in spite of* repeated perturbations on shorter time scales, or (b) the perturbations induced by contractures or other intrauterine events might in fact *contribute* to the global stability of CM. That is, we may be inclined to view the suite of stimuli associated with contractures as a potentially disrupting influence on fetal neurobehavioral organization. However, the fact that these (and other) sources of perturbation collectively constitute a reliable feature of the expected environment of the fetus raises the possibility that they may have come to play an important role in the development and maintenance of global dynamic stability in CM.

The Loss of CM Complexity During Contractures

The most prominent feature of the response of CM to uterine contractures between 118 and 132 dGA is the transient decrease in the irregularity of both low- and high-frequency components. In terms of the spectral content of spontaneous fetal motor activity, this represents a transient loss of complexity during contractures. The increased strength of both components during contractures at 125 and 132 dGA, indicating that power was concentrated in narrower bands around the dominant frequencies, is consistent with a loss of complexity in the components of CM. By the end of gestation, CM complexity was unaffected by uterine contractures.

Based on experimental manipulations of intracranial pressure in fetal sheep between 123 and 137 dGA, Walker and Harding (1986) have suggested that fetal neuroelectric

changes during contractures might be the result of transient cerebral hypoxemia induced by increases in intracranial pressure, which may be caused by direct mechanical compression of the fetus (Shields & Brace, 1994). If transient cerebral hypoxemia is the mechanism by which fetal CM is altered, then the loss of complexity in spontaneous motor activity during contractures would have two important implications.

First, it would imply that the characteristic irregularity of CM does not merely reflect the activity of spinal motor circuits. Rather, the irregularity reflects the direct or indirect influence of normal brain activity. Preliminary calculations using data from the rat fetus (Robertson & Smotherman, 1990b), human infant (Robertson et al., 1993), and sheep fetus (Robertson & Bacher, 1995) indicate that the complexity of CM reflects dynamic structure rather than noise. Taken together, these results suggest that an experimental analysis of the irregularity of spontaneous motor activity in the fetal sheep or rat might yield important information about the role of supraspinal sources in the dynamics of CM in these animals, and possibly in the human as well.

Second, the loss of CM complexity due to transient cerebral hypoxemia during uterine contractures would have practical implications as well. It would imply that the irregularity of the fluctuations in spontaneous motor activity might be a sensitive and rapidly responding indicator of the condition of the fetal central nervous system. This conclusion is consistent with previous arguments that organizational qualities of fetal behavior might reveal changes in fetal physiological status earlier and with greater sensitivity than the level or amount of activity (Bekedam, Visser, de Vries, & Prechtl, 1985; Ferrari, Cioni, & Prechtl, 1990; Prechtl, 1984, 1990).

CM Acceleration During Contractures

In addition to the prominent loss of CM complexity during contractures, there was some limited evidence at 118 dGA that CM also sped up. At 125 and 132 dGA there were no detectable changes in the rate of oscillation of either component. By the end of gestation, evidence for an increased rate of oscillation (especially in the high-frequency component) reappeared. It is possible that uterine contractures at 118 and 139 dGA altered the relative influence of local sources of oscillation in the motor system, with different preferred frequencies, on the overall rate of oscillation in CM.

In fetal rats, rostral sources of CM (in the brain and spinal cord above the midthoracic level) have a slower preferred frequency compared to sources in the caudal spinal cord (Robertson & Smotherman, 1990a). In the human neonate, transient motor activation induced by auditory stimulation leads to CM *slowing,* which may reflect the *increased* influence of slower rostral sources (Robertson, 1993a). If rostral sources are slower in the fetal sheep, as they are in the fetal rat, CM might accelerate if contractures increased the influence of caudal sources or decreased the influence of rostral sources. The latter possibility—decreased influence of rostral sources—might be expected if uterine contractures induce transient cerebral hypoxemia in the fetus (Jansen et al., 1979; Walker & Harding, 1986). It is unclear, however, why this effect was not observed at 125 and 132 dGA.

Nonlinearity and Characteristic Times in CM Response to Contractures

There was no evidence that the response of fetal CM to uterine contractures was systematically related to the duration or integrated amplitude of the contractures, or to the elapsed time since the preceding contraction, within the range of these variables

examined in this study. We used an operational definition of uterine contractures (>3 min of sustained uterine EMG activity above baseline) that is common in the recent literature. It is possible that a more graded response of fetal CM occurs to uterine activity that is sustained for less than 3 min or returns to baseline briefly one or more times during an otherwise continuous burst. Regardless of whether either of these possibilities occurs, our results indicate a strongly nonlinear response of fetal CM to the stimulation associated with contractures, with presumably maximal effects elicited by uterine activity that is sustained above baseline for approximately 3 min. Conditions established in the first few minutes of sustained uterine activity therefore appear to constitute the effective perturbation to the mechanism responsible for CM. This interpretation is consistent with evidence that elevated intracranial pressure lasting 60 s (caused by vena cava occlusion), or similar initial pressure changes that decrease gradually over 20–30 s (caused by extradural injection of saline) induce changes in fetal EOG, ECoG, and breathing (Walker & Harding, 1986).

Recovery of CM from the perturbation induced by contractures was rapid enough that the spectral properties of motor activity in the 10-min period immediately following the contractures were, in general, unchanged compared to precontracture values. Furthermore, there was no relation between the response of CM and the time since the previous contracture. For the data analyzed in this report, the interval between the onset of a usable contracture and the end of the preceding contracture (usable or not) could not be less than 5 min. Therefore, the characteristic time for CM to recover from the perturbation induced by uterine contractures is probably on the order of 5 min or less. This conclusion is consistent with the duration of neuroelectric effects triggered by experimental manipulations of intracranial pressure in fetal sheep (Walker & Harding, 1986).

Implications for Fetal Behavior and Development

The results demonstrate that a robust form of intrinsic temporal organization in spontaneous fetal behavior responds in a systematic manner to dynamic aspects of the intrauterine environment. The changes in spontaneous motor activity (particularly the loss of complexity) might, in turn, influence the extent to which the fetus samples and responds to other forms of stimulation. There is preliminary evidence in the fetal rat, for example, that adaptive responding to an ecologically relevant form of stimulation (grasping an artificial nipple) depends on the variability of spontaneous motor activity in the seconds preceding the presentation of the stimulus (Reilly et al., 1995). Furthermore, if the changes in spontaneous activity during uterine contractures are secondary to transient cerebral hypoxemia, the central processing of stimulus information and the control of behavior might be directly affected. In general, some of the observed variation within and between individual fetuses in their behavioral responses to various forms of stimulation (e.g., Robinson et al., 1995) might be accounted for by the timing of the stimuli in relation to spontaneous uterine contractures.

We have focused on the *transient* effects of uterine contractures on fetal CM. But contractures occur relentlessly during many weeks of rapid fetal development, and there is some evidence for cumulative neuroelectric and endocrine effects when uterine activity is increased (Sadowsky et al., 1992; Sadowsky, Martel, Cabalum, Poore, & Nathanielsz, 1992). It is possible that the repeated and complex stimulation associated with normal amounts of uterine contractile activity during much of gestation, and its effects on spontaneous motor activity, play an important role in the normal course of

fetal behavioral development. The increased sensitivity of CM to uterine contractures between 125 and 132 dGA suggests that some of the long-term consequences, if they exist, might originate during this window of developmental time.

It may be particularly important that during this period of increased sensitivity it is the irregularity of CM that responds most reliably to uterine contractures. Irregular fluctuation is perhaps the most characteristic property of spontaneous behavior in the fetal and neonatal periods, and it appears to reflect important properties of the dynamics that govern CM before and after birth (Robertson, 1993b; Robertson et al., 1993). Furthermore, evidence is accumulating that the irregular fluctuations in spontaneous motor activity regulate infant's interactions with the physical and social world during at least the first few months after birth (Lalley, 1993; Robertson et al., 1995). Therefore, if exposure to repeated uterine contractures has more than transient effects on the complexity of spontaneous motor activity, the effects are likely to have widespread postnatal significance.

Notes

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