

Effects of Labor Contractions on Catecholamine Release and Breathing Frequency in Newborn Rats

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Plasma catecholamines in newborn rats (0–2 hr old) were analyzed following vaginal birth, cesarean section with simulated labor contractions, or cesarean section without labor contractions. Upon delivery, pups were exposed to key elements of the rat's natural birth process, that is, umbilical cord occlusion, tactile stimulation, and cooling. Only pups exposed to actual or simulated labor showed an immediate rise in norepinephrine and epinephrine. Initial postpartum respiratory frequencies were higher in vaginal than in cesarean delivered pups and, in all groups, inversely correlated with catecholamine titers, suggesting respiratory distress or transient tachypnea at lower catecholamine levels. These findings establish a rat model for analyzing effects of labor on neonatal adaptive response during the transition from prenatal to postnatal life.

Keywords: fetus, birth, respiration, norepinephrine, epinephrine

The metamorphosis from fetus to newborn constitutes the most profound developmental transformation in a mammal's life. Prior to birth, the mother contributes important resources (e.g., oxygen and glucose) that help maintain and regulate the fetus's physiological systems. During birth, placental connections to the mother are abruptly severed, thereby eliminating this major prenatal support system. To ensure its survival at birth, the newborn mammal must swiftly recruit a veritable constellation of novel physiological and behavioral responses. The onset of pulmonary respiration, reorganization of the heart and circulation, utilization of stored glycogen, and shift to acquiring sustenance from a maternal nipple constitute some of these vital postpartum adaptations.

It has been known for some time that labor contractions help the neonate adapt to the extrauterine world (Lagercrantz & Slotkin,

1986). Around the time of birth, the fetus experiences a multitude of strong pressures associated with labor contractions. During contractions, umbilical blood flow is intermittently constricted, and oxygen availability to the fetus waxes and wanes (Lagercrantz & Slotkin, 1986; Seidler & Slotkin, 1985). The fetus is repeatedly squashed and pitched by contractions strong enough to alter the shape of its head, then squeezed through the birth canal into a cold extrauterine milieu. These birth-related experiences elicit in the fetus a surge of catecholamines (Lagercrantz & Bistoletti, 1977), arising primarily from the adrenal gland and from the Organ of Zuckerkandl, a transient perinatal source of catecholamines (C. T. Jones, 1980; Phillippe, 1983). Newborns delivered by near-term elective cesarean section, during which labor is typically absent, show significantly lower plasma levels of norepinephrine and epinephrine as compared with vaginally delivered babies. In contrast, babies delivered by cesarean section after the onset of labor have profoundly elevated plasma catecholamines as compared with babies delivered by elective cesarean section (Irestedt, Lagercrantz, Hjemdahl, Hagnevik, & Belfrage, 1982). Apparently, the birth-related catecholamine surge confers upon newborns a number of important protections. As compared with babies exposed to a trial of labor, babies delivered by elective cesarean section (even near term) show (a) an increased risk of respiratory morbidity (Cohen & Carson, 1985; Zanardo et al., 2004); (b) a fivefold increase in the likelihood of persistent pulmonary hypertension (Levine, Ghai, Barton, & Strom, 2001); (c) lower dynamic lung compliance (Faxelius, Hagnevik, Lagercrantz, Lundell, & Irestedt, 1983) and higher functional residual capacity, possibly as an adaptation to elevated lung water content (Hagnevik, Lagercrantz, & Sjoqvist, 1991); (d) increased incidence of postpartum

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respiratory distress (Irestedt, Lagercrantz, & Belfrage, 1984); (e) decreased protection from oxidative stress (Buhimschi, Buhimschi, Pupkin, & Weiner, 2003); and (f) delayed neurodevelopmental status (Otamiri, Berg, Ledin, Leijon, & Lagercrantz, 1991; Otamiri, Berg, Ledin, Leijon, & Nilsson, 1990). Animal studies of labor's effects on the fetus and newborn, conducted almost exclusively in the precocial sheep fetus, have revealed important roles of birth-related catecholamines, including stimulating lung liquid absorption (reviewed by Barker & Olver, 2002), sustaining metabolic and cardiac homeostasis (Padbury et al., 1987), and providing protection from hypoxia (C. T. Jones, 1980).

Labor-induced catecholamine release may provide an important mechanism underlying the neonate's process of adapting to extrauterine conditions and the recruitment of vital postnatal behaviors (Ronca, Abel, & Alberts, 1996). In earlier studies of the rat, we reported that labor contractions are necessary for maintaining continuous postpartum breathing (Ronca & Alberts, 1995b), although physical stimulation (e.g., maternal licking or brush stroking) is sufficient for establishing sustained breathing in newborn pups (Ronca & Alberts, 1995a). We also found that simulated labor contractions more than double the likelihood that pups will first attach to the mother's nipple at 2 hr postpartum (Abel, Ronca, & Alberts, 1998) under thermal conditions mimicking the rat's natal environment in the laboratory setting (Alberts, Blumberg, & Ronca, 1991). Using remote video surveillance, we have described in detail the birth process in the rat from the offspring's perspective (Ronca, Lamkin, & Alberts, 1993). Behavioral expressions of labor are present 6 hr prior to the birth of the first pup. The rat dam vigorously licks each newborn pup as it emerges from the womb, cleansing it and removing its birth membranes. Immediately following this brief (2–3 min) period of maternal care, the dam ingests the placenta, then undergoes additional labor contractions until the birth of the next pup. Throughout labor and delivery, pups remain scattered throughout the bedding, exposed to room temperature. Using a thermographic imaging system, we determined that pups' surface temperatures plummet to room temperature (approximately 22 °C) within 15 min of their births (Alberts et al., 1991). It is not until the completion of the 60–90 min birth process that the dam retrieves pups into the nest and begins to warm them.

In the present experiment, we used our knowledge of rat birth to test the hypothesis that compressions associated with labor contractions elicit catecholamine release in the newborn rat. Our model simulates the mammalian birth process and preserves major ecological aspects of the rat's perinatal environment. In other words, we applied forms and levels of stimulation to which the perinatal rat is typically exposed during parturition and the period of early maternal care (Alberts et al., 1991; Ronca et al., 1993; Ronca & Alberts, 1994).

We simulated key elements of the vaginal birth process in near-term rat fetuses by systematically applying (a) artificial labor contractions, (b) umbilical cord occlusion, (c) postpartum cooling, and (d) simulated maternal licking. We compared groups of newborn rats that underwent normal vaginal delivery (vaginal), cesarean section following simulated uterine contractions (compressed), or cesarean section with no contractions (noncompressed). These conditions correspond in humans to vaginal birth, cesarean section with labor, and elective cesarean section without labor, respectively. Plasma norepinephrine and epinephrine were measured in groups of pups at each of six time intervals spanning 0–120 min postpartum. Because labor-induced lung liquid absorption is an

especially important aspect of respiratory adaptation in postpartum mammals (see Barker & Olver, 2002; Jain & Eaton, 2006, for review), we compared breathing frequencies of vaginal, compressed, and noncompressed pups beginning at 5 min postpartum.

Materials and Method

Animal experimentation was conducted in accordance with the guidelines of the Indiana University Institutional Animal Care and Use Committee and the National Research Council's (1996) *Guide for the Care and Use of Laboratory Animals*. Prenatal and newborn rats ($N = 612$, minimum 6 pups per condition) derived from 61 pregnant Sprague–Dawley dams (*Rattus norvegicus*; 80–100 days) bred at Indiana University were used. Nulliparous females were time-mated to Sprague–Dawley males and a daily vaginal lavage was performed. Gestational Day 0 of the rats' 22-day pregnancy corresponded to the day that spermatozoa were first observed. Pregnant dams were individually housed in maternity cages (47 cm × 26 cm × 21 cm) lined with corncob bedding and maintained under standard conditions (12-hr light–dark cycle [0600:1800], 21 °C). Purina Rat Chow (Purina Mills, St. Louis, MO) and water were available ad libitum.

Cesarean Delivery Procedure

These procedures are reported elsewhere (Abel et al., 1998; Ronca & Alberts, 1995a, 1995b). On Gestational Day 21, we briefly (<1 min) anesthetized pregnant rat dams with an isoflurane–oxygen mix (3%/L/min). A small (3-cm) incision was made over the lumbar (L) spinal vertebrae and a chemomyelotomy performed by injecting ethanol (100 μ l 100%) between L1 and L2. The dam was allowed to recover from general anesthesia, placed in a Plexiglas chair, and her lower body immersed into a warm (37.5 °C \pm 0.5 °C) buffered saline bath. A midline laparotomy was performed, and the uterine horns externalized into the bath.

Between 2 and 4 contiguous fetuses (beginning with the second uterine position from the ovary) derived from each uterine horn were used as subjects. Twenty minutes following anesthesia, a small, inflated latex balloon attached to a handheld gram scale was used to compress 4 fetuses within one uterine horn at a magnitude of 15 mmHg to approximate pressure measured during actual labor contractions (Ronca & Alberts, 1994). One 20-s compression was delivered each minute for 15 min. Fetuses in the opposite horn were not compressed. Assignment of horns to labor condition was counterbalanced across dams.

Following externalization, an incision was made along the antimesometrial border of the uterus, and 4 fetuses were delivered from each uterine horn onto a gauze pad. Each pup was stroked briefly (2 min) to mimic maternal licking and the umbilical cord ligated. Neonates were then placed on gauze pads in plastic containers.

Vaginal Delivery Procedure

On Gestational Day 21, dams were quietly observed every few hours for signs of labor (Ronca & Alberts, 1994), then every 15 min thereafter. For each pup, time of birth was recorded and the dam permitted to lick and handle the pup for 2 min. The pup was removed from the cage and placed on a gauze pad in a plastic container. Within each litter, between 2 and 4 consecutive pups were treated identically.

Postpartum Treatment of Cesarean and Vaginally Delivered Pups

Following delivery, there ensued a thermal regimen mimicking the natural sequence of postpartum temperature exposures within the nest (Alberts et al., 1991; Ronca et al., 1993), which typically involves evaporative cooling immediately after delivery and rewarming when the dam gathers and begins to brood the pups. Blood was collected at 0, 5, 30, 60, 90, or 120 min postpartum (hereafter referred to as T0, T5, T30, T60, T90,

and T120); thus the amount of time pups spent at a given temperature depended on the temporal condition to which they were assigned. For cesarean delivered groups, the 4 compressed subjects derived from a given uterine horn were randomly assigned to different temporal conditions; control fetuses from the opposite uterine horn received the same temporal assignment. Vaginally delivered pups were also randomly assigned to treatment conditions. Figure 1 illustrates the time points for data collection from pups relative to temperature exposures. Pups in the T0 through T60 groups were exposed to 22 °C until the time of blood collection, whereas pups in the T90 and T120 groups were exposed to 22 °C for the first postpartum hour, then exposed to typical nest temperature (33 °C) until the time of blood collection.

Blood was collected by live decapitation. To avoid collecting catecholamines released due to decapitation, we used only the first drop of blood for analysis (El-Khodor & Boksa, 2003). To attain sufficient plasma volume, we pooled samples from between 2 and 4 pups per condition. Pups were randomly assigned to conditions.

Breathing frequencies were analyzed by counting movements of the diaphragm for 1 min immediately prior to blood collection. Because breathing movements are infrequent at birth and the first postdelivery blood sample required immediate action, breathing was not quantified in the T0 condition.

Plasma Collection and Preparation

Immediately following blood collection, samples were centrifuged for 9 min at -7 °C and 2,050 RPM. Plasma was pipetted into a clean microtube and recentrifuged. Plasma was again transferred into a clean microtube and stored at -70 °C until analysis.

Catecholamine Analysis

Catecholamines were measured from small (25–100 μ l) plasma volumes (Gleeson, Dalessio, Carr, Wickler, & Mazzeo, 1993; Korzan, Summers, Ronan, & Summers, 2000; Lin et al., 1984). Acid-washed aluminum oxide (50 mg) was added to a 1.5-ml Sep-Pak filter cartridge (Waters Associates, Milford, MA). Internal standard DHBA (10 μ l, 100 ng/ml) and 100 μ l plasma was added. Immediately upon the addition of 1 ml Tris buffer (1.86 M, pH 8.65) samples were vortexed and capped, then rotated for 10 min, revortexed, and the supernatant was aspirated. The alumina was washed and vortexed four times with 1 ml H₂O and a small volume of pH 7 buffer, aspirated each time to near dryness. A microtube (200 μ l) was placed on the cartridge as a receiver tube and centrifuged to remove residual fluid. A new receiver tube was placed on the cartridge and 100 μ l 0.1N HClO₄ was added to the sample. Samples were vortexed for 30 s, allowed to stand for 3–5 min, and then revortexed. The cartridge and receiver tube were recentrifuged and recovered perchloric acid extract was frozen until analysis by high pressure liquid chromatography (HPLC; Waters Associates) with electrochemical detection. Perchloric acid extract was injected directly into the HPLC system and analyzed electrochemically with an

amperometric cell and LC-4B potentiostat (Bioanalytical Systems, West Lafayette, IN). The electrode potential was set at +0.575 V with respect to an Ag to Ag/AgCl₂ reference electrode. The mobile phase consisted of citric acid (14 g), sodium acetate (8.6 g), 1-octanesulfonic acid (sodium salt; 110–120 mg), ethylenediaminetetraacetic acid disodium salt (150 mg), and methanol (100 ml). Flow rate was 1.0 ml/min.

Statistical Analyses

We performed statistical comparisons with one-way analyses of variance (ANOVA) and Newman-Keuls post hoc tests. Pearson's correlation coefficient was used to determine relationships among dependent variables.

Results

Plasma catecholamine levels varied with birth mode and time following delivery. At T0, both norepinephrine and epinephrine were profoundly elevated in vaginal and compressed pups as compared with noncompressed pups (see Figure 2, norepinephrine, and Figure 3, epinephrine). A two-way ANOVA revealed a main effect of time, $F(5, 10) = 21.298, p < .0001$, and a Birth Mode \times Time interaction, $F(10, 203) = 2.441, p < .01$. Post hoc comparisons confirmed that at T0, vaginal and compressed pups differed significantly from noncompressed pups but not from one another ($p > .10$).

Plasma epinephrine levels reflected a similar effect of labor contractions on immediate postpartum catecholamines. Two-way ANOVA revealed a main effect of time, $F(5, 10) = 64.891, p < .0001$, and a Birth Mode \times Time interaction, $F(10, 204) = 3.778, p < .0001$. As with norepinephrine, post hoc comparisons indicated that pups in the vaginal and compressed conditions did not differ from one another, but both differed significantly ($p < .05$) from the noncompressed condition.

Breathing Frequency

For each birth condition, respiratory frequencies were slow for the first hour and increased two- to threefold at T90 and T120 (see Figure 4). A two-way ANOVA comparing breathing frequency for all groups revealed a main effect of birth mode, $F(2, 28) = 5.701, p < .01$, time, $F(4, 8) = 36.677, p < .0001$, and a Birth Mode \times Time interaction, $F(8, 167) = 3.119, p < .01$. Post hoc analyses revealed that, at T5 and T30, breathing frequencies of vaginal pups were significantly greater than those of compressed and noncompressed pups, whereas frequencies of compressed and noncompressed pups did not differ from one another. Respiratory frequen-

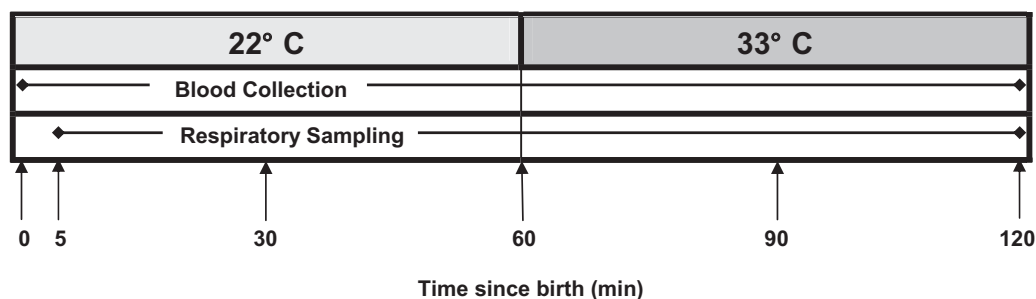


Figure 1. Ambient postpartum temperature in relation to time since birth (in minutes) for blood collection and respiratory sampling in vaginal, compressed, and noncompressed pups.

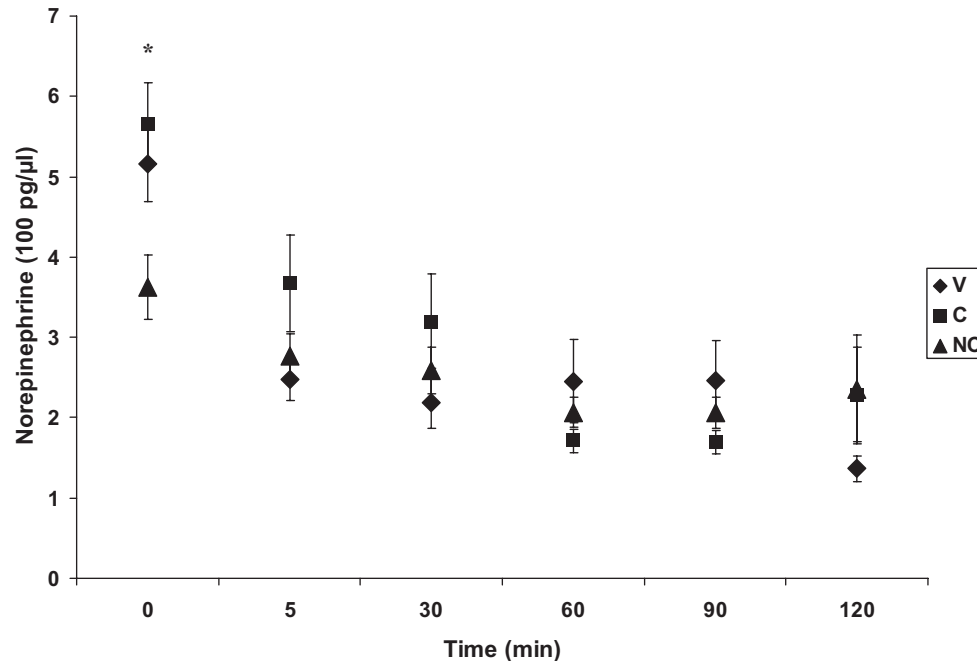


Figure 2. Postpartum plasma norepinephrine titers ($M \pm SEM$ in pg/100 μ l plasma) following either vaginal birth (V), cesarean birth with compressions (C), or cesarean birth with no compressions (NC) at 0, 5, 30, 60, 90, and 120 min postpartum. Pups in the V and C conditions were significantly different from pups in the NC condition at 0 min postpartum. * $p < .05$.

cies were similar for pups in all birth conditions during the second hour.

Relationships Between Respiratory Frequency and Catecholamines

For each birth condition, respiratory frequency was negatively correlated with release of norepinephrine and epinephrine across most of the time points (see Table 1). The relationship between norepinephrine and respiratory frequency achieved significance for all three groups at T5 and T30, whereas relationships for correlations for noncompressed pups were significant only late in the observation period (T120). An identical pattern of results was observed for epinephrine.

Discussion

Our major finding is that compressions mimicking labor contractions profoundly elevated immediate postpartum plasma norepinephrine and epinephrine to levels comparable to those of vaginally delivered pups and to levels more than 35% greater than those of noncompressed pups. This is the first demonstration of labor-elicited catecholamine release in the perinatal rat, and the findings parallel those reported in human studies and studies using the precocial sheep model (C. T. Jones, 1980; Lagercrantz & Bistoletti, 1977). It is important to note that our simulated birth model incorporates actual forms and levels of sensory and physiological stimuli to which the newborn rat is exposed during natural vaginal birth and allows us to specifically parcel out the effects of labor on postpartum functions. We believe that the findings re-

ported herein establish an ecologically valid paradigm for analyzing major sensory and biochemical effects of labor.

Pups in the compressed and vaginal groups showed strikingly similar catecholamine responses. This is particularly impressive because vaginal delivery involves far more labor contractions over a much longer period as compared with the trial of 15 simulated contractions we applied to compressed pups. Furthermore, this similarity was evident despite modest age differences between subjects in the compressed and vaginal groups. Whereas dams in the vaginal condition typically delivered their pups on the 22nd gestational day, cesarean deliveries were performed late on the rats' 21st gestational day, prior to the onset of natural labor. Taken together with previous reports (Abel et al., 1998; Ronca & Alberts, 1994, 1995a, 1995b), the present findings reaffirm the fidelity and relevance of our simulated birth model to vaginal birth. It is important to note that our results closely parallel reports of catecholamine release in human babies delivered vaginally, by cesarean section with labor, or by elective cesarean section without labor (Irestedt et al., 1982; C. M. Jones & Greiss, 1982; Jouppila, Puolakka, Kauppila, & Vuori, 1984; Wang, Zhang, & Zhao, 1999). This is true despite the fact that a rat's sympathetic-adrenal system is highly immature at birth compared with that of a human (Seidler & Slotkin, 1985).

The reduced breathing rates of compressed and noncompressed pups relative to vaginal pups at 5 and 30 min postpartum may reflect some factor common to the cesarean delivery procedure. Possibilities include (a) younger age (12–18 hr) of cesarean delivered newborns, (b) reduced ability to cope with the cool temperature, (c) prenatal exposure to isoflurane anesthesia, or (d) mater-

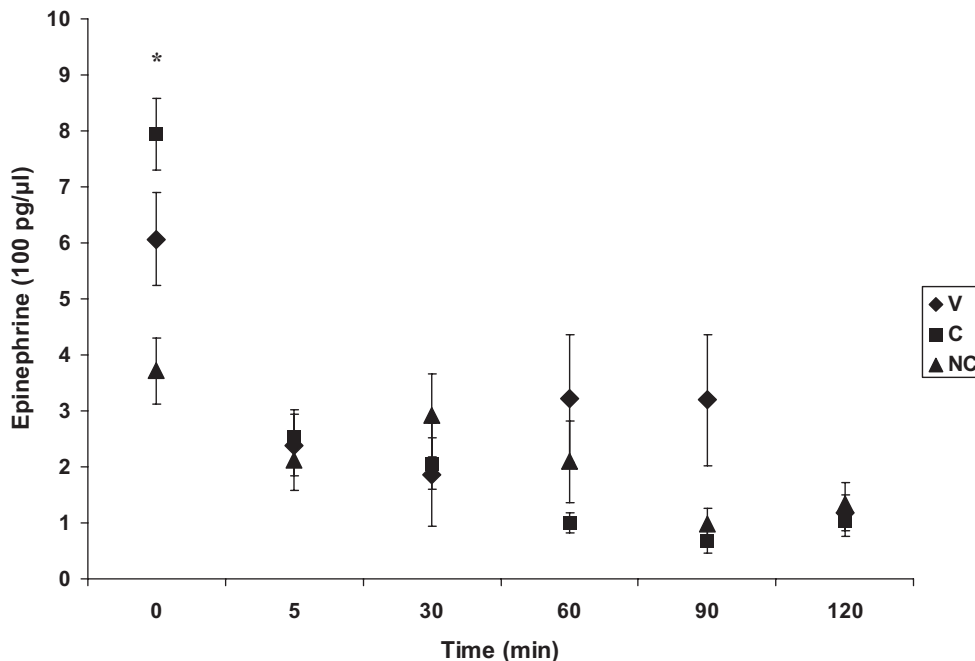


Figure 3. Postpartum plasma epinephrine titers ($M \pm SEM$ in $pg/100 \mu l$ plasma) following either vaginal birth (V), cesarean birth with compressions (C), or cesarean birth with no compressions (NC) at 0, 5, 30, 60, 90, and 120 min postpartum. Pups in the V and C conditions were significantly different from pups in the NC condition at 0 min postpartum. * $p < .05$.

nal or fetal response to the surgical manipulation. Although these specific comparisons are beyond the scope of this study, each presents an interesting and testable hypothesis amenable to further study.

At 60 min postpartum, the similar breathing frequencies of pups in all three conditions can be accounted for by a decline in breathing frequencies of vaginally delivered pups, likely related to the extended (1-hr) period of postnatal cooling. Increased breath-

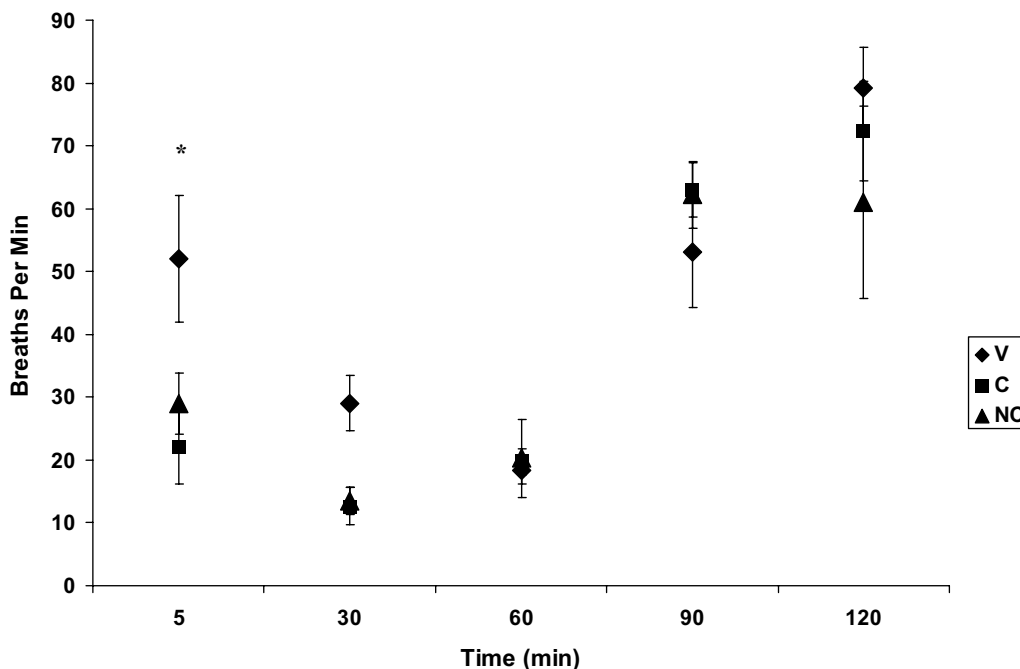


Figure 4. Respiratory movements of rat pups ($M \pm SEM$) at time 5, 30, 60, 90, or 120 min following either vaginal birth (V), cesarean birth with compressions (C), or cesarean birth with no compressions (NC). Pups in the V condition were significantly different from pups in the C and NC conditions at 5 min postpartum. * $p < .05$.

Table 1
Correlation Coefficients Between Norepinephrine and Respiratory Frequency and Epinephrine and Respiratory Frequency in Rat Pups in the Three Birth Conditions Over the First 2 Postpartum Hours

Birth condition	N	R ²	
		Norepinephrine	Epinephrine
Vaginal	49	-.165*	-.134*
Compressed	62	-.197*	-.221*
Noncompressed	70	-.170*	-.235*

Note. Compressed = delivered by cesarean section with compression; noncompressed = delivered by cesarean section without compression.

* $p < .01$.

ing rates for pups in all conditions coincided with warming of pups from 22 to 33 °C beginning during the second postpartum hour. Although we did not measure body temperature in this study, our observations of thermal effects on breathing are consistent with a previous study of neonatal rats that reported approximately 30% greater breathing frequencies at 30 and 37 °C as compared with 25 °C (Tattersall & Milsom, 2003). The major determining factor underlying these ventilatory changes is the metabolic response to body temperature (Mortola, 2005). Unlike adult mammals, the control of body temperature in altricial neonates is poorly developed, leaving them highly susceptible to hypothermia. The response is exacerbated under conditions of hypoxia, a phenomenon known as *hypoxic hypometabolism*, in which even mild hypoxic challenges exert effects on respiratory mechanical properties and aspects of ventilatory control persisting into adulthood (Mortola, 2004).

Elective cesarean section of human infants is associated with respiratory morbidity, including respiratory distress, transient tachypnea, hyaline membrane disease, and persistent pulmonary hypertension (Brice & Walker, 1977; Cohen & Carson, 1985; Faxelius, Bremme, & Lagercrantz, 1982; Levine et al., 2001; van den Berg, van Elburg, van Geijn, & Fetter, 2001; Usher, Allen, & McLean, 1971; Zanardo et al., 2004). In our study, despite the group differences in breathing frequencies early in the postpartum measurement interval, we observed in each birth condition inverse correlations indicating that low plasma catecholamines were associated with higher respiratory rates. This finding may reflect poorer lung liquid clearance leading to respiratory distress or transient tachypnea (also known as “wet lungs”; Jain & Eaton, 2006). Even in the vaginal delivery condition, low plasma catecholamines were associated with higher respiratory rates. One interpretation of this observation is that labor contractions exert natural variations in birth-related catecholamine release that may alter lung liquid clearance and surfactant release, thereby affecting postnatal respiratory variables (Barker & Olver, 2002). These observations fit well with the established relationship between lung liquid clearance and respiratory distress, including transient tachypnea of the newborn (Jain & Eaton, 2006).

It is unlikely that our noncompressed pups were more than mildly hypoxic. Both hypoxia and labor contractions evoke similar high levels of catecholamine release during birth, and we did not see catecholamine elevations in that group exceeding those of labor-exposed pups. Our findings are consistent with the idea that

catecholamine release in response to hypoxia causes long-term neural changes. Fetal oxygen deprivation, such as that which occurs with umbilical cord occlusion during labor, causes fetal distress. Male rat fetuses surgically delivered without labor showed reduced levels of plasma epinephrine at birth relative to vaginally born controls, whereas those surgically delivered with added 15-min anoxia had elevated plasma catecholamines postnatally (El-Khodor & Boksa, 2003), probably as a compensatory reaction to the period of acute anoxia. In addition, male rats surgically delivered (with or without anoxia and without exposure to labor contractions) showed increased brain lactate, indicative of mild central nervous system hypoxia, on the first day of life. El-Khodor and Boksa's study did not incorporate labor manipulations, thereby supporting the view that the absence of labor contractions is associated with adverse neonatal outcomes.

Labor appears to play a major role in the broad constellation of neural, physiological, and behavioral changes that occur at birth. These changes include pulmonary and respiratory variables (Cohen & Carson, 1985; Faxelius et al., 1983; Irestedt et al., 1984; Levine et al., 2001; van den Berg et al., 2001; Zanardo et al., 2004), blood flow (C. T. Jones, 1980; Irestedt et al., 1984), resistance to oxidative stress (Buhimschi et al., 2003), neonatal neurological condition (Otamiri et al., 1990, 1991), and complex global electroencephalogram patterns (Kim et al., 2003). Perinatal olfactory cues guide breast preferences (Varendi, Porter, & Winberg, 1994), and learning about olfactory cues is enhanced in neonates that experience labor contractions, possibly mediated by norepinephrine (Varendi, Porter, & Winberg, 2002). Together with the results reported herein, these studies support the view that prenatal events associated with labor initiate a cascade of neural, physiological, and behavioral events that assist the newborn infant's adaptation to the extrauterine world.

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