Influence of the Order of Birth on Blood Gasometry Parameters in the Fetal Neonatal Transitional Period of Dogs Born by Elective Caesarean Parturition

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ABSTRACT

The umbilical artery and jugular venous blood gases of the first five neonatal puppies born from nine healthy bitches by elective caesarean section, were analyzed to determine whether the order of birth had any influence over the evaluated parameters. Anesthesia was induced with propofol (6.0 mg kg-1, IV) followed by epidural injection of 2% lidocaine chloride (5.0 mg kg-1). Additional boluses of propofol (2.0 mg kg-1) were administered as needed. A blood sample (0.3 mL) was taken from the umbilical artery before the puppy took its first breath. Venous blood samples were obtained from the jugular vein of all neonates, 30 and 90 minutes after birth, for further blood gas analysis. There was no significant difference in pH (p=0.73), $PvCO_2$ (p=0.96), PvO_2 (p=0.55) and HCO_3 (p=0.99) between the averaged values of all five birth positions at moment 0' or when considering the combination of all moments evaluated (0', 30' and 90'): pH (p=0.83), $PvCO_2$ (p=0.96), PvO_2 (p=0.43) and HCO_3 (p=0.98). For puppies born by elective caesarean with this anesthetic protocol, the puppy's birth order did not influence blood gases.

INTRODUCTION

Various degrees of hypoxia and transitory interference in maternal-fetal respiratory exchange are common in all types of parturition1: normal parturition, elective cesarean section[2], partus induction[3] and dysfunctional labour[4]. Fetuses are able to tolerate considerable oxygen reduction[2], once the fetal buffering systems, most notably bicarbonate and hemoglobin, can maintain a normal pH for some time, forestalling the onset of acidemia[5]. In humans, relative lack of oxygen to the fetus over a critical length of time will cause a switch of the aerobic energy production to anaerobic glycolysis, resulting in the production of lactic acid and decrease in blood pH[6].

The physiological respiratory changes taking place in the first 90 minutes after birth, can be reflected in the blood gasometry of puppies born by elective caesarean parturition[7]. The umbilical cord consists of one vein and two arteries[8, 9] in its juxtafetal section. These vessels are responsible for blood exchange between the fetal and maternal organisms[9].Through cordocentesis, it is possible to evaluate the fetus' acid-base equilibrium and, indirectly, any respiratory depression caused, for example, by the transplacental passage of drugs[10].

During pregnancy fetal physiology is influenced by any drug administered to the mother, either directly, by the drug itself, or indirectly, as a result of maternal effects. All anesthetics are able to cross the placental barrier[11, 12, 13]. However, the rate of maternal hepatic metabolism and renal excretion of drugs may affect the amount of drugs to which the fetus is exposed[14].

A number of anesthetic drugs administered to the mother were associated with puppy vigor characteristics, like breathing, moving and vocalizing[15] and may be a cause of neonatal depression[11, 12, 13]. Drugs with high lipid solubility are able to cross the placenta into the fetus[16]. Propofol, a highly lipophilic anesthetic agent[17], has been the drug of choice in anesthesia induction for caesarean sections due to the minor fetal respiratory and cardiovascular depression it causes[11, 18]. Moreover, propofol has minimal effect on human maternal and fetal acid-base equilibrium[18, 19] and presents minimal residual effects on the fetuses[13]. Epidural anesthesia is also a good choice for caesarean sections, producing the least respiratory and neurologic depression in puppies when compared with injectable and inhaled anesthetics in the bitch[12, 13]. In elective caesareans, anesthesia induction and maintenance with propofol boluses, in conjunction with lidocaine or bupivacaine epidural, does not cause clinical signs of neonatal depression in dogs[20].

The time between anesthesia induction for the caesarean section and the puppy removal from uterus should be the least possible. The shorter the exposure of the fetuses to the anesthetics, the greater the probability of them being viable at birth[14]. Since acid-base equilibrium regulation is one of the main factors for maintaining organ equilibrium, any problem in this process, when taking place during the perinatal period, may result in irreversible consequences to the newborn[21]. Therefore the objective of this work was to examine whether the puppy's birth order (1st, 2nd, 3rd, 4th and 5th) influences venous blood gas analysis of dogs born by elective caesarean-section, from bitches anesthetized and maintained with propofol and epidural lidocaine in the first 90 minutes after birth.

EXPERIMENTAL PROCEDURE

Nine mixed breeds clinically healthy pregnant bitches were enrolled in the study. All dogs were between 1-3 years old and had body weight between 10-25 kg. All bitches were monitored from approximately half-way through pregnancy using weekly ultrasound examinations, until the end of the gestation (59 to 62 days after mating). The scheduling of the caesarean section was based on the clinical data obtained from weekly examinations. An abdominal radiographic examination was performed after aproximately 50 days of gestation, in the dorsoventral and lateral positions, in order to certify that there were at least five fetuses.

At the surgical center, each female had a cephalic venous catheter placed, which was connected to an infusion set containing a 0.9% physiological solution and maintained with a continuous infusion (30 mL.kg-1. hour-1). Anesthesia was induced with 6.0 mg kg-1 of propofol IV (Abbott)8 followed by epidural blockade with 2% lidocaine chloride (5.0 mg kg-1)20. Additional boluses of propofol (2.0 mg kg-1)[8], were administered as needed throughout the surgical procedure.

After the onset of epidural anesthesia[22], the surgical procedure was iniciated. Fetuses were removed first from the right uterine horn, then from the left one[23]. The females were monitored using a Vital Signs Monitor (Life Window LW 6.000 – DIGICARE), throughout the whole surgical procedure.

***Table 1**. Descriptive analysis of **pH** for all five puppy positions at moments 0', 30' and 90'. Different letters in the same column differ statistically.*

Position (birth order)	Time	n	Mean ± SD (min; max)
1st a	pH 0 pH 30 pH 90	9 9 9	7.21 ± 0.08 (7.07; 7.30)[a] 7.21 ± 0.09 (6.98; 7.28)[a] 7.30 ± 0.08 (7.17; 7.41)[b]
2nd a	pH 0 pH 30 pH 90	8 8 8	7.15 ± 0.08 (7.04; 7.30)[a] 7.17 ± 0.11 (7.00; 7.31)[a] 7.30 ± 0.05 (7.25; 7.37)[b]
3rd a	pH 0 pH 30 pH 90	9 9 9	7.14 ± 0.07 (7.02; 7.21)[a] 7.15 ± 0.10 (6.95; 7.25)[a] 7.30 ± 0.06 (7.19; 7.42)[b]
4th a	pH 0 pH 30 pH 90	9 9 9	7.16 ± 0.10 (6.98; 7.28)[a] 7.19 ± 0.09 (7.05; 7.29)[a] 7.31 ± 0.06 (7.21; 7.43)[b]
5th a	pH 0 pH 30 pH 90	9 9 9	7.18 ± 0.07 (7.04; 7.31)[a] 7.17 ± 0.12 (6.95; 7.27)[a] 7.31 ± 0.07 (7.19; 7.40)[b]

***Position** = order of birth: 1st , 2nd , 3rd , 4th and 5th from the same female; n = number of puppies in each group; SD= standard deviation; **pH 0** = pH corresponding to the blood sample collected from the double-clamped umbilical cord, before the neonate took its first breath; **pH 30** = pH corresponding to the blood sample collected from the left jugular vein of each neonate, 30 minutes after birth; **pH 90** = pH corresponding to the blood sample collected from the right jugular vein of each neonate, 90 minutes after birth.*

***Table 2**. Descriptive analysis of **$PvCO_2$** for all five puppy positions at moments 0', 30' and 90'. Different letters in the same column differ statistically.*

Position (birth order)	Time	n	Mean ± SD Variance (min; max) (mmHg)
1st a	$PvCO_2$ 0 $PvCO_2$ 30 $PvCO_2$ 90	9 9 9	60.67 ± 7.60 (51; 72)[a] 57.67 ± 16.27 (47; 99)[b] 45.33 ± 9.34 (35; 60)[c]
2nd a	$PvCO_2$ 0 $PvCO_2$ 30 $PvCO_2$ 90	8 8 8	59.25 ± 9.53 (46; 74)[a] 55.00 ± 15.96 (38; 90)[b] 45.25 ± 9.88 (30; 58)[c]
3rd a	$PvCO_2$ 0 $PvCO_2$ 30 $PvCO_2$ 90	9 9 9	61.67 ±14.53 (46; 92)[a] 53.67 ± 14.56 (37; 89)[b] 47.56 ± 7.02 (36; 57)[c]
4th a	$PvCO_2$ 0 $PvCO_2$ 30 $PvCO_2$ 90	9 9 9	57.56 ± 8.47 (50; 74)[a] 52.89 ± 11.55 (44; 80)[b] 44.11 ± 4.73 (35; 50)[c]
5th a	$PvCO_2$ 0 $PvCO_2$ 30 $PvCO_2$ 90	9 9 9	58.78 ± 9.20 (45; 73)[a] 57.11 ± 16.16 (44; 96)[b] 46.44 ± 9.13 (36; 63)[c]

***Position** = order of birth: 1st , 2nd , 3rd , 4th and 5th from the same female; n = number of puppies in each group; SD= standard deviation; **$PvCO_2$ 0** = PvCO2 corresponding to the blood sample collected from the double-clamped umbilical cord, before the neonate took its first breath; **$PvCO_2$ 30** = $PvCO_2$ corresponding to the blood sample collected from the left jugular vein of each neonate, 30 minutes after birth; **$PvCO_2$ 90** = $PvCO_2$ corresponding to the blood sample collected from the right jugular vein of each neonate, 90 minutes after birth.*

Table 3. *Descriptive analysis of* $\boldsymbol{PvO_2}$ *for all five puppy positions at moments 0', 30' and 90'. Different letters in the same column differ statistically*

Position (birth order)	Time	n	Mean ± SD Variance (min; max) (mmHg)
1st a	$PvCO_2$ 0 $PvCO_2$ 30 $PvCO_2$ 90	9 9 9	18.22 ± 3.46 (13; 23)[a] 21.89 ± 6.81 (17; 39)[b] 27.22 ± 7.73 (21; 44)[c]
2nd a	$PvCO_2$ 0 $PvCO_2$ 30 $PvCO_2$ 90	8 8 8	19.63 ± 13.45 (9; 52)[a] 19.63 ± 6.14 (14; 33)[b] 21.75 ± 4.27 (17; 31)[c]
3rd a	$PvCO_2$ 0 $PvCO_2$ 30 $PvCO_2$ 90	9 9 9	15.56 ± 2.07 (14; 19)[a] 21.00 ± 4.90 (14; 31)[b] 25.22 ± 5.07 (17; 35)[c]
4th a	$PvCO_2$ 0 $PvCO_2$ 30 $PvCO_2$ 90	9 9 9	16.89 ± 4.11 (11; 23)[a] 24.78 ± 7.55 (16; 36)[b] 25.89 ± 7.66 (17; 44)[c]
5th a	$PvCO_2$ 0 $PvCO_2$ 30 $PvCO_2$ 90	9 9 9	19.44 ± 4.00 (13; 25)[a] 23.56 ± 6.71 (14; 31)[b] 27.67 ± 4.82 (19; 35)[c]

Position *= order of birth: 1st , 2nd , 3rd , 4th and 5th from the same female; n = number of puppies in each group; SD= standard deviation;* $\boldsymbol{PvO_2}$ ***0*** *=* PvO_2 *corresponding to the blood sample collected from the double-clamped umbilical cord, before the neonate took its first breath;* $\boldsymbol{PvO_2}$ ***30*** *=* PvO_2 *corresponding to the blood sample collected from the left jugular vein of each neonate, 30 minutes after birth;* $\boldsymbol{PvO_2}$ ***90*** *=* PvO_2 *corresponding to the blood sample collected from the right jugular vein of each neonate, 90 minutes after birth.*

Table 4*. Descriptive analysis of* $\boldsymbol{HCO_3}$ *for all five puppy positions at moments 0', 30' and 90'. Different letters in the same column differ statistically.*

Position (birth order)	Time	n	Mean ± SD Variance (min; max) (mmHg)
1st a	HCO_3 0 HCO_3 30 HCO_3 90	9 9 9	22.78 ± 3.46 (15; 27) 22.22 ± 2.28 (19; 27)[a] 23.22 ± 4.18 (13; 27)[b]
2nd a	HCO_3 0 HCO_3 30 HCO_3 90	8 8 8	22.75 ± 4.20 (14; 28) 21.75 ± 3.69 (17; 27)[a] 24.38 ± 2.39 (21; 27)[b]
3rd a	HCO_3 0 HCO_3 30 HCO_3 90	9 9 9	22.56 ± 3.13 (16; 26) 21.33 ± 2.06 (18; 24)[a] 24.11 ± 2.26 (21; 28)[b]
4th a	HCO_3 0 HCO_3 30 HCO_3 90	9 9 9	22.78 ± 3.46 (16; 27) 21.56 ± 2.83 (17; 25)[a] 23.44 ± 1.74 (20; 26)[b]
5th a	HCO_3 0 HCO_3 30 HCO_3 90	9 9 9	23.11 ± 2.62 (18; 26) 21.67 ± 3.12 (18; 27)[a] 24.11 ± 3.18 (18; 28)[b]

Position *= order of birth: 1st , 2nd , 3rd , 4th and 5th from the same female; n = number of puppies in each group; SD= standard deviation;* $\boldsymbol{HCO_3}$ ***0*** *=* HCO_3 *corresponding to the blood sample collected from the double-clamped umbilical cord, before the neonate took its first breath;* $\boldsymbol{HCO_3}$ ***30*** *=* HCO_3 *corresponding to the blood sample collected from the left jugular vein of each neonate, 30 minutes after birth;* $\boldsymbol{HCO_3}$ ***90*** *=* HCO_3 *corresponding to the blood sample collected from the right jugular vein of each neonate, 90 minutes after birth.*

The time between maternal anesthesia induction and the removal of the fifth puppy was recorded, as well as the time between removal of the first and fifth puppies.

As each fetus was exteriorized from the uterus with its placenta, the amniotic sac was ruptured and its fluid removed[23]. Two hemostats were placed on the umbilical cord and, using a plastic 1.0 mL syringe and needle (0.38 x 13mm), previously rinsed with heparin24 at approximately 4% dilution (0.011 ± 0.0011mL), previously determined by weighing the syringe before and after the addition of heparin[25]. Cordocentesis was immediately performed between the hemostats[9], obtaining a blood sample (0.3 mL) from one of the umbilical arteries of each conceptus[26]. The blood samples were collected anaerobically and immediately sealed with cork, so as to avoid blood gas tension alteration. The syringe was rolled between the palms of the hands after the blood sample was obtained, so that it would mix with the anticoagulant[24]. This procedure was done before each neonate took its first breath. An incision was made between the hemostats and the neonates were then handed over to an assistant.

The neonate's respiratory tract was immediately cleared using sterile surgical gauzes while the head was inclined downwards, with the posterior limbs elevated, allowing for all the mucus and fluid from the respiratory tract to be drained. Respiration was stimulated by rubbing gauze over the thoracic region[27]. The umbilical cord was then tied at a 2.0 cm distance from the body, using a monofilament nonabsorbable suture (ETHICON, 3-0). The nine females delivered a total of 70 puppies, from which only the first five puppies of each female were included in the analysis in order to standardize the number of puppies per female, giving a total of 45 puppies to analyze. The neonates were then identified by a numbered tag attached to their tails, according to the order of birth, and placed on a thermal cushion. The following physiological and vigor signs were observed and recorded for each neonate: temperature, spontaneous breathing, movement and vocalization. Other normal reflexes were verified for each neonate right after birth: suckling, neck extension, urination, righting, nociceptive withdrawal and magnus reflexes.

Other 0.3 mL venous blood samples were obtained from the jugular vein of all neonates, 30' and 90' minutes after birth. All blood samples were identified and stored at 4°C23 until the laboratory analysis, within 30 minutes of its collection.

Samples were analyzed individually by the blood gas and pH Analyzer (Radiometer Copenhagen Model ABLTM5). For the first neonatal sample, collected from the umbilical cord before its section, the apparatus was calibrated to venous blood, 37°C temperature, 12 mg dL-1 hemoglobin and 21% oxygen concentration fraction of inspired gas. As for the two other neonatal samples, the same parameters were used, except for the temperature, which was reduced to 35°C20.

The repeated measures analysis of variance (ANOVA) with one factor was performed to verify the influence of the position (1st, 2nd, 3rd, 4th and 5th), time (0', 30', 90') and position-time interaction in the measures for pH, $PvCO_2$, PvO_2 and HCO_3. Differences were considered statistically different if $P<0.05$. The statistical analysis was processed by the statistics software SAS® System.

RESULTS AND DISCUSSION

The average time between maternal anesthesia induction and the removal of the 5th puppy was 23 minutes. The average time between the removal of the 1st and the 5th puppy, respectively, was 10 minutes. The number of animals was reduced from 45 to 44 puppies, since the second puppy born from female number 2 died at 33 minutes after birth, and so its data were removed from the records.

The mean body temperature for the bitches at the moment of the first blood sample collection was of $37°C \pm 0.246$. The average hemoglobin of most females on the day of the surgery was 12 mg dL-1 hemoglobin ± 0.876. All of the 44 puppies included in this study had a mean body temperature of 35ºC ± 0.196 prior to the second (30') and third (90') sample collection. Vigor evaluation showed spontaneous breathing, vocalization and normal responses for suckling, neck extension, urination, righting, nociceptive withdrawal and magnus reflexes for all puppies born at the immediate post-natal period.

Tables 1, 2, 3 and 4 provide mean, standard deviation (SD), and minimum and maximum values of pH, $PvCO_2$, PvO_2 and HCO_3, respectively, throughout the three times being evaluated, for all five puppy birth orders.

All of the 44 puppies presented similar variations in the evaluated parameters (pH, $PvCO_2$, PvO_2 e HCO_3) throughout moments 0', 30' and 90', independent of birth order. There was no significant differences in pH at moments 0' and 30', increasing significantly in all puppies at moment 90' (Table 1). While $PvCO_2$ reduced (Table 2), PvO_2 increased (Table 3) gradually in each evaluated moment in all five birth orders. HCO_3 presented significant differences at moments 30' and 90' for every puppy, independent of birth order, having increased significantly at moment 90' (Table 4).

Results of the repeated measures analysis of variance for pH, $PvCO_2$, PvO_2 and HCO_3 are presented in Table 5. The values in the table correspond to the level of significance of each component (birth order, time and birth order-time interaction). The repeated measures ANOVA showed no significant difference for pH (p=0.73), $PvCO_2$ (p=0.96), PvO_2 (p=0.55) and HCO_3 (p=0.99) according to the order of birth. No significant difference was observed in pH (p=0.83), PvCO2 (p=0.96), PvO_2 (p=0.43) and HCO_3 (p=0.98) between the five birth orders throughout the evaluated times (0', 30', 90').

The results demonstrate that, for puppies born by elective caesarean parturition, with propofol induction and maintenance, and lidocaine epidural anesthesia, the time taken to remove the 5th puppy, after removal of the 1st, did not affect the evaluated measurements (pH, PCO_2, PO_2 and HCO_3) (Table 1-4), or alter neonate vigor in the immediate post-natal period. Therefore, the order of removal of each puppy did not influence the studied measures.

All anesthetics are able to cross the placental barrier[11, 12, 13]. However, the rate of placental diffusion and the depression that may potentially be caused is dependent on a series of factors inherent or not to the drugs used[28]. The similar evolution of the hemogasometric parameters found for the 1st and 5th puppies can be justified by the pharmacological characteristics of the anesthetic drugs used on the mother. Even though propofol is a highly lipophilic anesthetic agent[17], and therefore is capable of crossing the placental barrier into the fetuses16, it presents a rapid onset and short time of action[17, 13], causes minor fetal respiratory and cardiovascular depression[11], and promotes minimum residual effect to the fetuses[13]. Similarly, epidural anesthesia produces minimal respiratory side effects in puppies born by elective cesarean parturition[12, 13]. Moreover, during the additional 10-minute period

Table 5. *Results of the Repeated Measures Analysis of Variance of the evaluated parameters **(pH, $PvCO_2$, PvO_2** and **HCO_3**), giving the level of significance (p-values) of each component (position, time and position-time interaction).*

Variable	Position (birth order)	Time (minutes)	Interaction (position-time)
pH	0.73	0.0001	0.83
$PvCO_2$ (mmHg)	0.96	0.0001	0.96
PvO_2 (mmHg)	0.55	0.0001	0.43
HCO_3 (mmol/L)	0.99	0.0004	0.98

during which the 5th puppy awaited removal from the uterus, its circulation remained connected to that of the bitch, which continued to participate in the metabolization of the circulating drugs[14]. This may justify the similarity in pH, $PvCO_2$, PvO_2 and HCO_3 evolution found between the five birth orders for moment 0' (Tables 1-4). The similar evolution of these parameters, however, for the five birth orders in moments 30' and 90', indicate that the additional time to which the last fetus was exposed to the anesthetics was not enough to alter the hemogasometric parameters during the transition of the fetal-neonatal period.

When a human is positioned in dorsal recumbency, the compression made by the pregnant uterus on the caudal vena cava and aorta may cause a severe deficit in cardiac output, systemic arterial hypotension, reduction of uterine blood flow and fetal anguish[29]. Some authors believe that this same effect can be found in animals[11]. Considering this to be true, it seems logical to assume that the fifth puppy to be removed from the uterus should present a higher $PvCO_2$ at moment 0' than the first puppy. However, there was no significant difference in the values of $PvCO_2$ for the five birth orders (Table 2). It may be suggested that, in this experiment, time spent in this position was not enough to cause a considerable difference in oxygen transfer through blood flow in the additional 10 minutes during which the 5th puppy awaited removal from the uterus. Additionally, some authors believe that there seems to be a much greater available collateral circulation in dogs so that positioning the animal in dorsal recumbency is less likely to have a negative effect[30].

It is known that fetuses possess protective mechanisms that allow them to endure some reductions in placental oxygen tension. During the fetal stage, hemoglobin has a greater affinity for oxygen, which means that, given the same oxygen tension, fetal blood is capable of transporting more oxygen than maternal blood. The fetal heart can work without oxygen for longer periods than that of an adult, since the fetal myocardial cells contain relatively great quantities of glycogen. Moreover, fetal tissues are more resistant to hypoxia than those of an adult. These factors allow for an adequate oxygenation of fetal tissues despite the lower oxygen tension of the blood arriving from the placenta[31]. The additional 10 minutes the 5th puppy remained in the uterus, as compared to the 1st puppy, did not significantly influence the blood oxygen results (Table 3). This finding suggests that either the oxygen tension was not low enough to cause alterations in the evaluated parameters, or that the physiological mechanisms mentioned above were able to compensate for the lower oxygen tension, or even that the fetuses were able to reduce their oxygen consumption maintaining similar values for the observed parameters, despite the extra time in a condition of lower oxygen tension. However, caution must be taken in these assumptions, and further studies are necessary in order to effectively evaluate the degree of oxygen consumption by the fetus under conditions of low oxygen tension.

Fetal respiratory acidosis develops when there is a reduction in the oxygen supply to the fetuses during a short period of time. When the oxygen shortage occurs over a longer period of time, the nature of the acidosis changes from respiratory to metabolic and the fetus substitutes the aerobic energy production for anaerobic glycolysis, resulting in lactic acid accumulation, more accentuated blood pH reduction and increase in base deficit[1, 6]. The results of this experiment did not show any differences in the blood gas results obtained from the fetal blood samples collected by cordocentesis, where the order of birth was considered.

CONCLUSION

It was concluded that, the time taken to remove the 5th puppy, after removal of the 1st, being that of 10 minutes, did not affect the evaluated measurements (pH, PCO2, PO2 and HCO_3). The evolution of the parameters throughout the 90 minutes was statistically similar in all puppies indicating that the additional 10-minute period during which the 5th puppy awaited removal from the uterus did not interfere on its capacity for hemogasometric adaptation to extra-uterine life. In addition, neonatal vigor at immediate post-natal period was similar to all five puppies born by elective caesareans under this anesthetic protocol, independent of the birth order.

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