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Review

PROLONGED SECOND STAGE LABOUR AND CONSEQUENCES OF HYPOXIA IN THE NEONATE: A REVIEW

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Summary

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Hypoxia due to dystocia and its repercussions are serious issues concerning the health of neonates. In order to gain a better understanding of the cause and especially the effects and potential long-term disorders, a critical analysis of peer-reviewed literature was made. As shown by many authors, initially the most devastating peripartal cause of ill health in neonates is associated with the serious effects of prolonged and severe acidosis. Other life threatening complications are related to disorders such as meconium aspiration syndrome (MAS), neonatal respiratory distress syndrome, hypoxic ischaemic encephalopathy and necrotising enterocolitis. Despite the astonishing ability of neonates to compensate mixed metabolic and respiratory acidosis with breathing onset directly postpartum, the longer second stage labour takes and the more extreme the acidosis is, the more detrimental its consequences. Lungs are especially vulnerable in this phase of life, aspired meconium can result in increased expression of pro-inflammatory chemotactic cytokines, phospholipase A_2 and PGE_2 levels , exacerbating inflammatory reactions of lung tissue and exerting a deleterious effect on alveolar cells. Neonates experiencing dystocia could greatly benefit from administration of buffering substances and non-steroidal anti-inflammatory drugs.

Key words: acidosis, foetal stress, hypoxia, meconium, neonates

INTRODUCTION

Neonatal mortality in farm animals continues to be high, so from an economic and animal welfare perspective a high motivation exists to reduce this death rate. One major cause of neonatal death is intra-uterine hypoxia during second stage labour. The aim of this review is to elucidate the patho-physiological mechanisms of hypoxia and its negative effects on vitality of neonates with focus on the lungs.

FOETAL/PERINATAL METABOLISM. BLOOD GAS AND ACID-BASE DYNAMICS AT PARTURITION

Eutocia

Foetal growth and vitality depend on the supply of nutrients and oxygen and removal of metabolic wastes and carbon dioxide made possible through the intricate relationship between mother, placenta and foetus (Tucker & Hauth, 1990; Mota-Rojas *et al.*, 2011). With the onset of second stage labour the umbilical cord is temporarily occluded during abdominal contractions and the placental membranes begin detaching. This causes a disruption in the blood flow through the placenta depriving the foetus from oxygen as well as nutrients (Walser & Maurer-Schweizer, 1978; Rurak *et al.*, 1990; Tucker & Hauth, 1990; Alonso-Spilsbury *et al.*, 2005; Castro-Najera *et al.*, 2006; Taverne & Noakes, 2009). The circulatory disruption of the uteroplacental unit causes a mixed metabolic respiratory acidosis.

Walser & Maurer-Schweizer (1978) as well as Rurak *et al.*, (1990) and some others affirm that the physiological hypoxia and hypercapnia experienced by the foetus during birth, makes it switch to oxygen-saving circulation sparing the heart, central nervous system (CNS) and adrenal gland.

During the perinatal period and shortly after birth the foetus and then the neonate depends on its hepatic glycogen reserves, gluconeogenesis and switches to anaerobic metabolic pathways to sustain itself, which causes an increase in lactic acid resulting in a metabolic acidosis (Walser & Maurer-Schweizer, 1978; Patterson *et al.*, 1987; Szenci, 2012; Bleul & Götz, 2013). This anaerobic phase also causes a mild respiratory acidosis reflected in a decreased blood pH and an increased base deficit (Comline & Silver, 1972; Busse *et al.*, 1986; Kumar & Paterson-Brown, 2010). At birth all vital functions such as blood oxygenation, pH maintenance, thermoregulation and normoglycaemia are transferred over to the neonate. The respiratory acidosis, hypercapnia, is a major incentive to begin breathing, necessary for subsequent independent life. Thrifty neonates have an astonishing ability to self-correct metabolic and respiratory imbalances due to hypoxia, with the respiratory component subsiding quickly and the metabolic component: within 24– 48 hours (Comline & Silver, 1972; Walser & Maurer-Schweizer, 1978; Bostedt & Bellinghausen, 1985; Busse *et al.*, 1986; Szenci *et al.*, 1988; Herpin *et al.*, 1996; Varga *et al.*, 2001; Gorlt, 2004; Richter, 2005; Walser, 2009; Poulsen *et al.*, 2009; Schultz, 2009; Taverne & Noakes, 2009; Blomhoff Holm, 2012; Bleul & Götz, 2013). Table 1 shows an overview of the literature on pH, pCO_2 and base excess (BE) values in different neonates.

Acid-base status in eutocia

Blood pH values of neonates are a well-established parameter measured to assess the thriftiness of newborn infants. Comline & Silver (1972) and Busse *et al.* (1986) presented similar findings in their studies with thrifty lambs, and demonstrated that blood pH around parturition was < 7.20 and 7.18, respectively. Both research teams also showed that once breathing was established, the pH normalised quickly, within 30–60 minutes and 12 hours respectively. Several authors showed that thrifty neonates begin life with blood pH below average spanning from 7.20 to 7.31 and pCO_2 above average, 51.0 to 70.4 mmHg (Table 1). The cause of the abnormal blood parameters is

Table 1. Overview of pH, pCO_2 and BE in thrifty bovine and equine neonates (v=venous blood, a=arterial blood)

Reference	Animal species	Mean blood pH	pCO_2 (mmHg)	BE (mmol/L)
Walser & Maurer-Schweizer (1978)	bovine	ca. 7.20 (v) 15 min. *p.n.*	ca. 65	ca. –4
Bostedt & Bellinghausen (1985)	equine	ca. 7.25 (v) at birth	67	large individual variance
Szenci *et al.* (1988)	bovine	7.31(v) at birth	51.0*	0
Herfen (1999)	bovine	7.28 (v) at birth	62.58	0.40
Varga *et al.* (2001)	bovine	7.26 (a) 5 min. *p.n.*	59.8	–2.3
Gorlt (2004)	equine	7.27 (v) at birth	70.38	2.42
Richter (2005)	bovine	7.28 (a) at birth	63.46*	0.97
Bleul & Götz (2013)	bovine	7.24 (v) 10 min *p.n.*	61.35	–2.5

*converted from kilopascals into millimeters mercury (Szenci *et al.*, 1988: 6.8 kPa; Richter, 2005: 8.46 kPa; factor 7.5006168).

a mixed metabolic and respiratory acidosis caused by the birthing process. Most authors affirm that the respiratory component subsides faster, according to others – the metabolic acidosis was more important but all agree that the mixed respiratory metabolic acidosis due to labour is a physiological aspect of birthing and is usually alleviated within 24 hours *post natum* (*p.n.*) (Comline & Silver, 1972; Walser & Maurer-Schweizer, 1978; Bostedt & Bellinghausen, 1985; Busse *et al.*, 1986; Szenci *et al.*, 1988; Herpin *et al.*, 1996; Varga *et al.*, 2001; Gorlt, 2004; Richter, 2005; Bleul & Götz, 2013).

During birth when the blood supply through the foetal-placental unit is intermittent the neonate is not only deprived of oxygen, but also of glucose and other nutrients (Mota-Rojas *et al.*, 2011). The foetus and then the neonate maintains *intra partum* normoglycaemia via anaerobic glycolysis owing to its hypoxic state, causing an accumulation of lactic acid (Szenci, 2012; Bleul & Götz, 2013). Lactic acid is the major metabolite responsible for decreased pH resulting in metabolic acidosis. The BE, a calculated value, allows determining whether an acidosis is metabolic (Busse *et al.*, 1986; Bleul & Götz, 2013). Busse *et al.* (1986) demonstrated that thrifty lambs had a moderate negative BE which normalised within four hours *p.n.*, most thrifty lambs even showed a positive BE 24 hours *p.n.*. Bostedt & Bellinghausen (1985) also showed that the BE, which had the highest individual variability, steadily rose far above zero until the fourth day of life. Glucose levels in all foals were at the lower limit of the reference range increasing continuously with the commencement of suck-

ling. The drop in glucose in the first half hour of life is noteworthy, showing how quickly glucose reserves are exhausted and the dangers of inadequate suckling in the adaptation phase (Bostedt & Bellinghausen, 1985). Comline & Silver (1972) showed in their study with lambs that lactic acid began rising significantly one hour before parturition, reaching its maximum values 5–10 minutes *p.n.* The observations of Comline & Silver (1972) showed a close relationship between the peri-natal pH fall and lactic acid rise. They also showed that the glucose levels behaved similarly to the lactic acid levels with a peak immediately *p.n.* In their model with calves, Walser & Maurer-Schweizer (1978) demonstrated that the acidosis worsened in the first 10–15 minutes of life although thrifty neonates began breathing immediately after birth. They attributed this to the abolition of the oxygen-saving circulation, funneling oxygenated blood to the CNS, heart, and adrenal gland and the subsequently increased circulating lactic acid. Bleul & Götz (2013) also observed increased L-lactate and pCO_2 concentrations in thrifty calves, but a constant pH, disagreeing with Comline & Silver (1972). These values normalised within 48 and 4 hours, respectively.

Dystocia

A delayed or difficult parturition, dystocia, leads to a protracted expulsion and invariable hypoxia (Lombard *et al.*, 2007; Taverne, 2008). If hypoxia persists due to dystocia it could have serious negative long-term effects on the survival of the neonate or be immediately fatal (Adams *et al.*, 1991; Lopez & Bildfell, 1992; Lombard *et al.*, 2007; Bleul *et al.*, 2010; Blomhoff Holm, 2012; Barrier *et al.*, 2013). The cumulative effects of uterine contractions by pathologically prolonged labour, will lead to cord damage or rupture as well as premature detachment of the placenta (Herpin *et al.*, 1996; Vaala, 1999; Taverne, 2008). In the late 70's Walser & Maurer-Schweizer (1978) discussed the dangers of neonatal hypoxia, resulting in acidosis, which ultimately leads to death of individual cells. Szenci *et al.* (1988) and Walser & Maurer-Schweizer (1978) pointed out that a pH of 6.7 wass incompatible with life. Acidosis which is the most severe in disorders such as meconium aspiration syndrome, hypoxic-ischaemic encephalopathy or enterocolitis and potentially death, is often a consequence of dystocia (Vaala, 1999; Ikeda *et al.*, 2000; Martinez-Burnes *et al.*, 2002; Castro-Najera *et al.*, 2006; Katz, 2006; Vidyasagar & Zagariya, 2008; Kumar & Paterson-Brown, 2010; Jacobson Misbe *et al.*, 2011; Mokra & Mokry, 2011; Armstrong *et al.*, 2012). Mota-Rojas *et al.* (2005) showed in a study with 120 farrowing sows, through the administration of oxytocin, that enhanced myometrium contractions caused severe foetal distress with decreased foetal heart rates and increased meconium staining, leading to higher intra-partum mortality. Cord rupture facilitated placental detachment by causing a decrease in blood pressure and a collapse of the chorionic villi (Alonso-Spilsbury *et al.*, 2005). Failure to establish breathing immediately after birth sustains the hypoxia-induced perinatum vasoconstriction of the lungs, intestines, kidneys, muscles and skin while keeping the blood flow to the CNS, heart and adrenal glands steady (oxygen-saving circulation) (Walser & Maurer-Schweizer, 1978; Rurak *et al.*, 1990; Weinberger *et al.*, 2001; Martinez-Burnes *et al.*, 2002; Alonso-Spilsbury *et al.*, 2005; Szenci, 2012; Bleul & Götz, 2013). This redistribution ensures the function of vital organs

of the hypoxic foetus. Any form of dystocia can be the cause of extended labour, facilitating prolonged hypoxia, hypercapnia and acidosis (Adams *et al.*, 1991; Lombard *et al.*, 2007; Schulz, 2009; Bleul *et al.*, 2010; Dutra & Banchero, 2011; Barrier *et al.*, 2013).

Events causing pathological hypoxia are:

- premature ablation of the placenta (Vaala, 1999; Alonso-Spilsbury *et al.*, 2005);
- inadequate placenta perfusion, e.g. uterine torsion, maternal hypotension (Alonso-Spilsbury *et al.*, 2005; Castro-Najera *et al.*, 2006);
- prolonged umbilical occlusion, e.g. sternal presentation (Alonso-Spilsbury *et al.*, 2005; Schulz, 2009);
- foetal-maternal disproportion, e.g. heifer, male calf (Berglund *et al.*, 2003; Mee *et al.*, 2008);
- mal-presentation , -position, -posture (Schulz, 2009).

Acid-base status in dystocia

Busse *et al.* (1986) showed that unthrifty lambs exhibited only slight variations in the acid/base and blood gas homeostasis, the steep and severe drop in pH in the first 15 minutes of life was due to the insufficient respiratory response of the lambs. Unthrifty lambs showed pH levels of 7.08 on the average and a much longer period of convalescence than thrifty lambs. Unthrifty lambs that died within 24 hours of parturition showed diverging severity of acidosis, but all had in common a drastic drop in pH minutes after birth, with venous blood pH remaining extremely low until the fatal outcome. Highly significant differences in venous pH levels between the thrifty and unthrifty lambs could be shown up until 4 hours *p.n*.

Gorlt (2004), Richter (2005), Herfen (1999) and Varga *et al.* (2001) showed that neonates experiencing prolonged birth due to dystocia were distinctly less thrifty then eutotic young. They displayed noticeably low blood pH ranging from 7.03 to 7.26. These animals had reduced respiratory activity, it took much longer to regulate their breathing rate and depth.

In contrast to other studies, in a study on 117 newborn piglets Herpin *et al.* (1996) reported that glucose levels were dramatically increased in neonates with prolonged parturition and showing unthriftiness. They surmised this to the increased secretion of stress hormones, such as catecholamines. The glucose utilisation due to reduced insulin secretion during hypoxia was still limited, available only to organs whose glucose uptake was insulin independent such as the CNS.

Walser & Maurer-Schweizer (1978) and later Bleul & Götz (2013) showed an increase in the pCO_2 and the lactic acid directly *p.n.* due to reduced respiratory activity and the reperfusion of peripheral organs, having a deleterious effect on depressed neonates.

Busse *et al.* (1986) reported similar findings where the BE declined sharply (–12 mmol/l) and the pCO_2 rose drastically (84 mmHg) within 15 minutes *p.n.*, owing to the inadequate respiratory response of the unthrifty lambs. The BE was normalised within 12 hours after birth and then reached positive values within 24 hours. Herfen (1999) confirmed a continuous drop in the BE within 10 minutes *p.n.* by up to 1.7 units establishing a direct correlation to the blood pH dynamics. Table 2 shows an overview of the results from previous studies.

When an organism falls in a hypoxic state, lactic acid is accumulated causing metabolic acidosis (Poulsen & McGuirk,

Table 2. Overview of pH, pCO_2 and base excess (BE), in unthrifty neonates (v=venous blood, a=arterial blood, n.a.=not available)

Reference	Animal species	Mean blood pH	pCO_2 (mmHg)	BE (mmol/L)
Walser & Maurer-Schweizer (1978)	bovine	ca. 7.09 (v)	ca. 74	ca. –10
Szenci *et al.* (1988)	bovine	7.14 (v)	66.76*	–6.0
Herfen (1999)	bovine	7.11 (v)	81.14	–6.9
Varga *et al.* (2001)	bovine	7.10 (a)	64.5	–10.9
Gorlt (2004)	equine	7.26 (v)	72.76	2.5
Richter (2005)	bovine	7.14 (a)	65.56*	–7.6
Bleul & Götz (2013)	bovine	7.03(v) 10 min p.p.	72.1	n.a.

*converted from kilopascals into millimeters mercury (Szenci *et al.,* 1988: 8.9 kPa; Richter, 2005: 8.74 kPa).

2009; Bleul & Götz, 2013). Reduced myocardial contractility, hypotension and eventual coagulopathies are the sequelae of the inevitable systemic metabolic acidosis (Seri & Evans, 2001). The decline in pH will cause cell injury in multiple organs and the oxygen insufficiency will force a shift to an anaerobic metabolism (Alonso-Spilsbury *et al.,* 2005; Bleul & Götz, 2013). Meconium staining of the neonate or the amniotic fluids is a sign of peripartal distress.

EFFECTS OF PATHOLOGICAL HYPOXIA ON THE ORGANS

Oxygen deprivation (hypoxia) triggers a cascade of cellular biochemical events bringing about an alteration in cell function, as far as cell death (Galvin & Collins, 2004; Alonso-Spilsbury *et al.*, 2005; Alonso-Alconada *et al.*, 2012). The cell loses its ability of efficient oxidative phosphorylation. The adenosine triphosphate (ATP) dependent sodium pump fails, exchange of ions across the cell membrane is disrupted and metabolites accumulate causing damage to the structural and enzymatic integrity of the cell (Blomhoff Holm, 2012). A similar devastating effect has the overproduction of free radicals followed by oxidative stress and increased stimulation of pro-inflammatory cytokines (Alonso-Alconada *et al.*, 2012). This multi-factorial process acts synergistically leading eventually to cellular necrosis (Alonso-Spilsbury *et al.* 2005).

Peri-partal hypoxia has various degrees of multisystemic effects (Vaala, 1999). Meconium staining of amniotic fluid is a macroscopic clinical sign for intrauterine hypoxia, foetal stress in animals as well as humans. Hypoxia experienced *in utero* causes an increased peristalsis of the intestines and a relaxation of the anal sphincter as well as increased respiratory movements resulting in the passage of meconium into the amniotic fluid causing a staining of the neonate and potential aspiration (Vaala, 1999; Martinez-Burnes *et al.*, 2002; Castro-Najera *et al.*, 2006; Mota-Rojas *et al.*, 2012; Swarnam *et al.*, 2012).

Lungs

The lungs develop in six stages, beginning as a ventral diverticulum in the foregut

endoderm and completing their development after birth (Pringle, 1986; Caswell & Williams, 2007). The lung progresses through phases of development, going through a series of epithelial-mesenchymal changes. The airway basement membrane region consists of three layers – the lamina lucida, lamina densa, lamina reticularis, and can be stained using the digested Periodic Acid-Schiff (PAS) reaction. Interstitial widening and increased cellularity are normal histological findings in children. Therefore it can be assumed that this would also pertain to neonatal animals (Colby *et al.*, 2007). The bronchus-associated lymphoid tissue (BALT) is not present at birth, becoming established with increasing age. Lymphocytes are generally only present and grouped together in a pathological state in neonatal lungs (Colby *et al.*, 2007). The mucosal epithelium of the conducting airways shows great cell diversity, depending upon the species and section of airways under consideration.

The lungs of most neonates continue to mature after partus, not being fully developed at birth (Pringle, 1986; Haworth & Hislop, 2003). The stage of microvascular maturation of the lung is a period of maturation of the air-blood interface, with a single capillary layer, which occurs after birth in nidicolous animals and peripartum in nidifugous animals (Roth-Kleiner & Post, 2003; Caswell & Williams, 2007).

Normal term foetuses may exhibit a minor sloughing of epithelial cells, but large amounts, especially if meconium is also present, indicate aspiration of amniotic fluid. This is a sign for increased intrauterine respiratory movement due to *in utero* hypoxia. Hypoxia can also be responsible for weak respiratory movement *p.n.* causing patchy congenital atelectasis due to incomplete expansion of the lung. Acute hypoxia due to prolonged parturition may be the cause of MAS. Histological sections of affected lungs show amorphous yellow-orange meconium, keratin, and/or squamous epithelial cells. This is associated with atelectasis, haemorrhage, and a mild but diffuse alveolar infiltration of neutrophils, macrophages, and occasionally multinucleate cells (Martinez-Burnes *et al.*, 2002; Satas *et al.*, 2003; Caswell & Williams, 2007; Poulsen & McGuirk, 2009; Mokra & Calkovska, 2013). Satas *et al.* (2003) showed that global hypoxia ischaemia produced multiple small haemorrhages as well as deposition of fibrin debris in the alveoli.

Lungs are affected by prolonged uterine hypoxia, first mechanically through the aspiration of meconium contaminated amniotic fluid and second, on a cellular level due to the anaerobic metabolism (Alonso-Spilsbury *et al.*, 2005; Bleul & Götz, 2013).

Lung macrophages are activated by prolonged hypoxia episodes increasing the production and release of inflammatory mediators. This initiates the inflammatory cascades ending in the release of reactive oxygen and nitrogen species that can damage pulmonary cells (Weinberger *et al.*, 2001; Mokra & Calkovska, 2013).

With the onset of breathing *p.n.*, the neonatal lungs experience increased alveolar oxygen tension and ensuing oxidative stress. The response of the organism is increased antioxidant defense, which is negatively influenced by pre-/perinatal hypoxic stress (Giles *et al.*, 2002).

Neonates born with MAS experience respiratory distress, the clinical signs are caused by airway obstruction, impaired gas exchange, atelectasis or dystelectasis, pneumonia and/or surfactant dysfunction (Vaala, 1999; Zagariya *et al.*, 2000). These structural and functional alterations

have in turn major effect on the acid-base regulation resulting in acidosis (Lopez & Bildfell, 1992). Clinical effects are not limited to the respiratory tract, since the acidosis and hypoxia affect all tissues in the body. Histological examinations of lungs from neonates that experienced respiratory distress from prolonged labour demonstrated squamous epithelial cells, meconium and inflammation after haematoxylin and eosin staining (Lopez & Bildfell, 1992). Zagariya *et al.* (2000) showed in a rabbit pups model that meconium triggers an increased polymorphonuclear leukocytes response of the lung tissue.

Intrapulmonary neutrophil accumulation greatly increased the expression of pro-inflammatory chemotactic cytokines, phospholipase A_2 and levels of PGE_2, exacerbating inflammatory reactions of lung tissue and exerting a deleterious effect on alveolar cells (Zagariya *et al.*, 2000; Vidyasagar & Zagariya, 2008; Mokra & Mokry, 2011). These inflammatory reactions caused increased vascular permeability leading to pulmonary oedema, proteinaceous exudate accumulation in the alveoli and an increased release of oxidative species potentially initiating increased apoptosis (Kirimi *et al.*, 2003; Vidyasagar & Zagariya, 2008).

CLINICAL CONSEQUENCES OF PATHOLOGICAL HYPOXIA

Prolonged intra-partum hypoxia causes unthriftiness, delayed first contact with the udder and weak suckling. This has negative effects on colostrum intake and causes a failure of passive transfer leading to hypogammaglobulinaemia and increased risk of infection, hypoglycaemia as well as a reduced absorption of other vital nutrients and minerals (Grongnet, 1984; Lopez & Bildfell, 1992; Alonso-Spilsbury *et al.*, 2005; Lombard *et al.*, 2007; Barrier *et al.*, 2013). Low glucose and high lactate levels due to anaerobic metabolism and depleted hepatic glycogen can often be associated with depression of the neonates (Walser, 2009; Mota-Rojas *et al.*, 2011). In his work with bovine neonates Linke (2013) showed that at the end of the first hour *p.n.* the lungs of thrifty born calves are still not fully ventilated, up to 80% cranially and 55% ventrally. It can be expected that the lungs of depressed neonates, which show lower respiratory activity, prolonged laying periods and incomplete left-right shunting of the cardio-vascular system, are even more poorly ventilated (Linke, 2013). Further diagnostic examinations with ultrasound, as established by Jung (2002), clearly showed increased atelectasis of the lungs by neonates that are unthrifty and showed clinical signs of amniotic fluids aspiration at birth. Some pathologies as pneumonia, hypoxic ischaemic encephalopathy, neonatal respiratory distress syndrome (nRDS), MAS, heart disease and necrotising enterocolitis are also commonly seen in neonates that experienced prolonged hypoxic episodes during birth (Touloukian *et al.*, 1972; Donnelly *et al.*, 1980; Clark *et al.*, 1988; Lopez & Bildfell, 1992; Vaala, 1999; Ikeda *et al.*, 2000; Zagariya *et al.*, 2000; Satas *et al.*, 2003; Canpolat *et al.*, 2006; Taylor & Colgan, 2007; Faa *et al.*, 2012; Lu *et al.*, 2012).

CONCLUSION

Dystocia will always be a major risk during birth, it is therefore essential to minimise these hazards to reduce neonatal losses. To this end, it is indispensable to detect, identify and alleviate pathologies during birth in a timely manner. A good pregnancy monitoring should be ensured,

combined with, when necessary, competent and professional assistance to increase survival chances and prevent disorders such as nRDS. This includes a targeted treatment with buffering substances and non-steroidal anti-inflammatory drugs, as well as oxygen supplementation and other reanimation measures.

REFERENCES

Adams, R., M. D. Holland, B. Aldridge, F. B. Garry & K. G. Odde, 1991. Arterial blood sample collection from the newborn calf. *Veterinary Research Communications*, **15**, 387–394.

Alonso-Alconada, D., E. Hilario, F. J. Alvarez, J. Francisco & A. Alvarez, 2012. Apoptotic cell death correlates with ROS overproduction and early cytokine expression after hypoxia-ischemia in fetal lambs. *Reproductive Sciences*, **19**, 754–763.

Alonso-Spilsbury, M., D. Mota-Rojas, D. Villanueva-Garcia, J. Martinez-Burnes, H. Orozco, R. Ramirez-Necoechea, A. L. Mayagoitia & M. E Trujillo, 2005. Perinatal asphyxia pathophysiology in pig and human: A review. *Animal Reproduction Science*, **90**, 1–30.

Armstrong, K., O. Franklin, D. Sweetman & E. J. Molloy, 2012. Cardiovascular dysfunction in infants with neonatal encephalopathy. *Archives of Disease in Children*, **97**, 372–375.

Barrier, A. C., M. J. Haskell, S. Birch, A. Bagnall, D. J. Bell, J. Dickinson, A. I. Macrae & C. M. Dwyer, 2013. The impact of dystocia on dairy calf health, welfare, performance and survival. *The Veterinary Journal*, **195**, 86–90.

Berglund, B., L. Steinbock, & M. Elvander, 2003. Causes of stillbirth and time of death in Swedish Holstein calves examined post mortem. *Acta Veterinaria Scandinavica,* **44**, 111–120.

Bleul, U. & E. Götz, 2013. The effect of lactic acidosis on the generation and compensation of mixed respiratory-metabolic acidosis in neonatal calves. *The Veterinary Record*, **172**, 528.

Bleul, U., B. Bircher, R. S. Jud & A. P. N. Kutter, 2010. Respiratory and cardiovascular effects of doxapram and theophylline for the treatment of asphyxia in neonatal calves. *Theriogenology*, **73**, 612–619.

Blomhoff Holm, M., 2012. The foetal response to acute perinatal hypoxia and the pathophysiological mechanisms behind hypoxic – ischemic encephalopathy. Dissertation, Faculty of Medicine, Oslo University.

Bostedt, H., & W. Bellinghausen, 1985. Blutgasanalysen und Substratbestimmungen bei neugeborenen Fohlen. *Tierärztliche Umschau*, **40**, 454–458.

Busse, G., H. Bostedt & A. Sobiraj, 1986. Ergebnisse der Blutgasanalytik bei neugeborenen Lämmern unter besonderer Berücksichtigung der neonatalen Atemdepression. *Deutsche Tierärztliche Wochenschrift*, **93**, 281–344.

Canpolat, F. E., M. Yurdaök, S. Özsoy, R. Hazıroğlu & A. Korkmaz, 2006. Protective effects of recombinant human granulocyte colony stimulating factor in a rat model of necrotizing enterocolitis. *Pediatric Surgery International,* **22**, 719–723.

Castro-Najera, J. A., J. Martinez-Burnes, D. Mota-Rojas, H. Cuevas-Reyes, A. Lopez, R. Ramirez-Necoechea, R. Gallegos-Sagredo & M. Alonso-Spilsbury, 2006. Morphological changes in the lungs of meconium-stained piglets. *Journal of Veterinary Diagnostic Investigation*, **18**, 622–627.

Caswell, J. L. & K. J. Williams, 2007. Respiratory system. In: *Jubb, Kennedy & Palmer's Pathology of Domestic Animals,* vol. 2, 5th edn, ed M. G. Maxie, Elsevier Saunders, Edinburgh, pp. 524–650.

Clark, D. A., D. M. Fornabaio, H. McNeill, K. M. Mullane, S. J. Caravella & M. J. Miller, 1988. Contribution of oxygen-derived free radicals to experimental necrotizing enterocolitis. *American Journal of Pathology,* **130**, 537–542.

Colby, T. V., K. O. Leslie & S. A. Yousem, 2007. Lungs. In: *Histology for Pathologists*, 3rd edn, ed S. E. Mills, Lippincott Williams & Wilkins, Philadelphia, pp. 437–504.

Comline R. S. & M. Silver, 1972. The composition of foetal and maternal blood during parturition in the ewe. *Journal of Physiology*, **222**, 233–256.

Donnelly, W. H., R. L. Bucciarelli & R. M. Nelson, 1980. Ischemic papillary muscle necrosis in stressed newborn infants. *The Journal of Pediatrics,* **96**, 295–300.

Dutra, F. & G. Banchero, 2011. Polwarth and Texel ewe parturition duration and its association with lamb birth asphyxia. *Journal of Animal Science,* **89**, 3069–3078.

Faa, A., N. Iacovidou, T. Xanthos, A. Locci, P. Pampaloni, F. Aroni, A. Papalois, G. Faa & V. Fanos, 2012. Hypoxia/reoxygenation-induced myocardial lesions in newborn piglets are related to interindividual variability and not to oxygen concentration. *Clinics,* **6**, 503–508.

Galvin, N. & D. Collins, 2004. Perinatal asphyxia syndrome in the foal: Review and a case report. *Irish Veterinary Journal,* **57**, 707–714.

Giles, B. L., H. Suliman, L. B. Mamo, C. A. Piantadosi, T. D. Oury & E. Nozik-Grayck, 2002. Prenatal hypoxia decreases lung extracellular superoxide dismuates expression and activity. *American Journal of Physiology – Lung Cellular and Molecular Physiology,* **283**, 549–554.

Gorlt, R., 2004. Untersuchung zum Blutgas- und Säure-Basen-Status beim neugeborenen Fohlen mittels netzunabhängiger Messmethode unter Berücksichtigung des Giessener Vorsorgeprogramms. Doctoral thesis, Justus-Liebig University, Giessen.

Grongnet, J. F., 1984. Metabolic consequences of induced hypoxia in newborn lambs. *Annales de Recherches Vétérinaires,* **15**, 17–28.

Haworth, S. G. & A. A. Hislop, 2003. Lung development – the effects of chronic hypoxia. *Seminars in Neonatology*, **8**, 1–8.

Herfen, K., 1999. Zur Säure-Basen-Statuts bei neugeborenen Kälbern in den ersten Lebenstagen unter besonderer Berücksichtigung differenter Vitalitätsstituationen. *Berliner und Münchener Tierärztliche Wochenschrift*, **112**, 166–171.

Herpin P., J. Le Dividich, J.C. Hulin, M. Fillaut, F. De Marco & R. Bertin, 1996. Effects of the level of asphyxia during delivery on viability at birth and early postnatal vitality of newborn pigs. *Journal of Animal Science*, **74**, 2067–2075

Ikeda, T., Y. Murata, E. J. Quilligan, J. T. Parer, T. Murayama & M. Koono, 2000. Histologic and biochemical study of the brain, heart, kidney, and liver in asphyxia caused by occlusion of the umbilical cord in near-term fetal lambs. *American Journal of Obstetrics and Gynecology,* **182**, 449–457.

Jacobson Misbe, E. N., T. L. Richards, R. J. McPherson, R. M. Burbacher & S. E. Juul, 2011. Perinatal asphyxia in a nonhuman primate model. *Developmental Neuroscience*, **33**, 210–221.

Jung, C., 2002. Sonographie der Lunge und des Abdomens beim bovine Neonaten unter besonderer Berücksichtigung pathologischer Veränderungen Doctoral thesis, Justus-Liebig University, Giessen.

Katz, L., 2006. Perinatal asphyxia syndrome in a quarter horse foal. *Veterinary Clinics of North America: Equine Practice*, **22**, 193–208.

Kirimi, E., O. Tuncer, M. Kosem, E. Ceylan, A. Tas, I. Tasal, R. Balahoroğlu & H. Caksen, 2003. The effects of prednisolone and serum malondialdehyde levels in puppies with experimentally induced meconium aspiration syndrome. *Journal of International Medical Research,* **31**, 113–122.

Kumar, S. & S. Paterson-Brown, 2010. Obstetric aspects of hypoxic ischemic encephalopathy. *Early Human Development*, **86**, 339–344.

Linke, B., 2013. Computer tomographic illustration of the development of the pulmonary function in bovine neonates until the twenty-first day postnatum. *Veterinary*

Medicine International, http://dx.doi.org/10.1155/2013/157960.

Lombard, J. E., F. B. Garry, S. M. Tomlinson, & L. P. Garber, 2007. Impacts of dystocia on health and survival of dairy calves. *Journal of Dairy Science*, **90**, 1751–1760.

Lopez, A. & R. Bildfell, 1992. Pulmonary inflammation associated with aspirated meconium and epithelial cells in calves. *Veterinary Pathology*, **29**, 104–111.

Lu, Y. Z., C. C. Wu, Y. C. Huang, C. Y. Huang, C. Y. Yang, T. C. Lee, C. F. Chen & L. C. H. Yu, 2012. Neutrophil priming by hypoxic preconditioning protects agains epithelial barrier damage and enteric bacteril translocation in intestinal ischemia/reperfusion. *Laboratory Investigation,* **92**, 783–796.

Martinez-Burnes, J., A. Lopez, G. M. Wright, W. P. Ireland, D. W. Wadowska & G. V. Dobbin, 2002. Microscopic changes induced by the intra-tracheal inoculation of amniotic fluid and meconium in the lung of neonatal rats. *Histology and Histopathology,* **17**, 1067–1076.

Mee, J. F., D. P. Berry & A. R. Cromie, 2008. Prevalence of, and risk factors associated with, perinatal calf mortality in pasture-based Holstein-Friesian cows. *Animal,* **2**, 613–620.

Mokra, D. & A. Calkovska, 2013. How to overcome surfactant dysfunction in meconium aspiration syndrome? *Respiratory Physiology & Neurobiology,* **187**, 58–63.

Mokra, D. & J. Mokry, 2011. Glucocorticoids in the treatment of neonatal meconium aspiration syndrome. *European Journal of Pediatrics*, **170**, 1495–1505.

Mota-Rojas, D., H. Orozco-Gregorio, D. Villanueva-Garcia, H. Bonilla-Jaime, X. Suarez-Bonilla, R. Hernandez-Gonzalez, P. Roldan-Santiago & M. E. Trujillo-Ortega, 2011. Foetal and neonatal energy metabolism in pigs and humans: A review. *Veterinarni Medicina*, **56**, 215–225.

Mota-Rojas, D., J. Martinez-Burnes, D. Villanueva-Garcia, P. Roldan-Santiago, M. E. Trujillo-Ortega, H. Orozco-Gregorio, H. Bonilla-Jaime & A. Lopez-Mayagoitia, 2012. Animal welfare in the newborn piglet: A review. *Veterinarni Medicina,* **57**, 338–349.

Mota-Rojas, D., J. Martínez-Burnes, M. E. Trujillo, A. López, A. M. Rosales, R. Ramírez, H. Orozco, A. Merino & M. Alonso-Spilsbury, 2005. Uterine and fetal asphyxia monitoring in parturient sows treated with oxytocin. *Animal Reproduction Science*, **86**, 131–141.

Patterson, D. J., R. A. Bellows, P. J. Burfening & J. B. Carr, 1987. Occurrence of neonatal and postnatal mortality in range beef cattle. I. Calf loss incidence from birth to weaning, backward and breech presentations and effects of calf loss on subsequent pregnancy rate of dams. *Theriogenology*, **28**, 557–571.

Poulsen, K. P. & S. M. McGuirk, 2009. Respiratory disease of the bovine neonate. *Veterinary Clinics of North America: Food Animal Practice*, **25**, 121–137.

Pringle, K., 1986. Human fetal lung development and related animal models. *Clinical Obstetrics & Gynecology*, **29**, 502–513.

Richter, B., 2005. Prognostische Aussagekraft arterieller gegenüber venöser Blutgasparameter im wiederholten Messrhythmus hinsichtlich des Schweregrades des neonatalen Atemnotsyndroms beim Kalb. Doctoral thesis, Justus-Liebig University, Giessen, 198 pages.

Roth-Kleiner, M. & M. Post, 2003. Genetic control of lung development. *Biology of the Neonate*, **84**, 83–88.

Rurak, D. W., B. S. Richardson, J. E. Patrick, L. Carmichael & J. Homan, 1990. Blood flow and oxygen delivery to fetal organs and tissues during sustained hypoxemia. *American Journal of Physiology*, **258**, R1116–R1122.

Satas, S., E. M. Loberg, H. Porter, A. Whitelaw, P. A. Steen & M. Thoreson, 2003. Effect of global hypoxia-ischaemia followed by 24 h of mild hypothermia on organ pathology and biochemistry in a newborn pig

survival model. *Biology of the Neonate,* **83**, 146–156.

Schultz, J., 2009. Prinzipien der Neonatologie. In *Geburtshilfe bei Haustiere*, 1st edn, eds W. Busch & J. Schulz, Enke, Stuttgart, pp. 159–175.

Schulz, J., 2009. Prinzipien der Neonatologie. In: *Geburtshilfe bei Haustiere*, 1st edn, eds W. Busch & J. Schulz, Enke, Stuttgart, pp. 159–175.

Seri, I. & J. Evans, 2001. Controversies in the diagnosis and management of hypotension in the newborn infant. *Current Opinion in Pediatrics,* **13**, 116–123.

Swarnam, K., A. S. Soraisham & S. Sivanandan, 2012. Advances in the management of meconium aspiration syndrome. *International Journal of Pediatrics,* http://dx.doi.org/10.1155/2012/359571.

Szenci, O., 2012. Diagnosis of perinatal well-being of dairy calves. *Lucrări Ştiinţifice - Seria Zootehnie*, **57**, 3–11.

Szenci, O., M. A. Taverne, S. Bakonyi & A. Erdödi, 1988. Comparison between pre- and postnatal acid-base status of calves and their perinatal mortality. *The Veterinary Quarterly*, **10**, 140–144.

Taverne, M. A., 2008. The relation between the birth process and the condition of the newborn piglet and calf. *Veterinary Research Communications*, **32,** Suppl 1, 93–98.

Taverne, M. & D. E. Noakes, 2009. Parturition and the care of parturient animals, including the newborn. In: *Veterinary Reproduction and Obstetrics*, eds. D. E. Noakes, T. J. Parkinson & G. C. W. England, 9th edn, Saunders/Elsevier, London, pp. 76–205.

Taylor, C. T. & S. P. Colgan, 2007. Hypoxia and gastrointestinal disease. *Journal of Molecular Medicine,* **85**, 1295–1300.

Touloukian, R. J., J. N. Posch & R. Spencer, 1972. The pathogenesis of ischemic gastroenterocolitis of the neonate: selective gut mucusal ischemia in asphyxiated neonatal piglets. *Journal of Pediatric Surgery,* **7**, 194–205.

Tucker, J. M. & J. C. Hauth, 1990. Intrapartum assessment of fetal wel-being. *Clinical Obstetrics and Gynecology*, **33**, 515–525.

Vaala, W. E., 1999. Peripartum asphyxia syndrome in foals. In: *Proceedings of the Annual Convention of the AAEP,* **45**, 247–253.

Varga, J., L. Mester, L. Börzsönyi, P. Lekeux & O. Szenci, 2001. Improved pulmonary adaptation in newborn calves with postnatal acidosis. *The Veterinary Journal*, **162**, 226–232.

Vidyasagar, D. & A. Zagariya, 2008. Studies of meconium-induced lung injury: Inflammatory cytokine expression and apoptosis. *Journal of Perinatology*, **28**, 102–107.

Walser, K. & H. Maurer-Schweizer, 1978. Die Asphyxie der Neugeborenen. *Tierarztliche Praxis*, **6**, 451–459.

Walser, K., 2009. Chapter 1.4 Atmung. In: *Neugeborenen- und Säuglingskunde der Tiere,* 1st edn, eds K. Walser & H. Bostedt, Enke Verlag, Stuttgart, pp. 14–18.

Weinberger, B., T. Carbone, S. England, A. M. Kleinfed, M. Hiatt & T. Hegyi, 2001. Effects of perinatal hypoxia on serum unbound free fatty acids and lung inflammatory mediators. *Biology of the Neonate,* **79**, 61–66.

Zagariya, A., R. Bhat, B. Uhal, S. Navale, M. Freidine & D. Vidyasagar, 2000. Cell death and lung cell histology in meconium aspirated newborn rabbit lung. *European Journal of Pediatrics,* **159**, 819–826.

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