The peripheral chemoreflex – indefatigable guardian of fetal physiological adaptation to labour

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Bio

Christopher Lear is a Research Fellow with the Fetal Physiology and Neuroscience Group, University of Auckland, New Zealand. His interests include the physiological adaptation to labour, and how understanding this fundamental physiology can improve the identification of fetuses at risk of hypoxic-ischemic brain injury.

Alistair Jan Gunn is a Paediatrician-scientist who has conducted ground breaking basic research into ways of identifying compromised fetuses in labour, the mechanisms and treatment of asphyxial brain injury and the mechanisms of life threatening events in infancy. He has helped to develop a range of new, clinically relevant chronically instrumented fetal sheep paradigms to support translation of the team's findings to clinical practice. His research helped to establish mild cooling as the first ever technique to reduce brain injury due to low oxygen levels at birth.

Abstract

The fetus is consistently exposed to repeated periods of impaired oxygen (hypoxaemia) and nutrient supply in labour. This is balanced by the healthy fetus's remarkable anaerobic tolerance, and impressive ability to mount protective adaptations to hypoxaemia. The most important mediator of fetal adaptations to brief repeated hypoxaemia is the peripheral chemoreflex, a rapid reflex response to acute falls in arterial oxygen tension. The overwhelming majority of fetuses are able to respond to repeated uterine contractions without developing hypotension or hypoxic-ischaemic injury. In contrast, fetuses who are either exposed to severe hypoxaemia, for example during uterine hyperstimulation, or enter labour with reduced anaerobic reserve (e.g., as shown by severe fetal growth restriction) are at increased risk of developing intermittent hypotension and cerebral hypoperfusion. It is remarkable to note that when fetuses develop hypotension during such repeated severe hypoxaemia, it is not mediated by impaired reflex adaptation, but by failure to maintain combined ventricular output, likely due to a combination of exhaustion of myocardial glycogen and evolving myocardial injury. The chemoreflex is suppressed by relatively long periods of severe hypoxaemia of 1.5 to 2 min, longer than the typical contraction. Even in this setting, the peripheral chemoreflex is consistently reactivated between contractions. These findings demonstrate that the peripheral chemoreflex is an indefatigable guardian of fetal adaptation to labour.

Introduction

Labour is inherently associated with intermittent 'asphyxia', as each intrapartum uterine contraction impairs gaseous exchange, with transient fetal hypoxaemia, hypercapnia and an obligatory shift to anaerobic metabolism, leading to metabolic acidaemia (Bax & Nelson, 1993). Uterine contractions reduce uteroplacental perfusion, as shown by reduced uterine artery blood flow velocity (Fleischer *et al.*, 1987; Janbu & Nesheim, 1987; Brar *et al.*, 1988; Li *et al.*, 2003) and reduced placental and intervillous perfusion (Ramsey, 1968; Sato *et al.*, 2016; Sinding *et al.*, 2016). Potentially, fetoplacental circulation may also be interrupted, secondary to compression of the umbilical cord. This is unlikely to occur due to increased amniotic pressure per se as the hydraulic pressure will be transmitted equally to the intra- and extravascular space, preventing any net compressive effect on the umbilical cord. Cord compression can occur during cord entanglement, knots or physical compression of the cord between the fetus and uterus. Fetoplacental perfusion may additionally be impaired due to upstream compression of the placental vasculature by uterine contractions. Although it is difficult to determine the cause of impaired fetoplacental perfusion in any individual labour, reduced perfusion appears to occur most commonly during contractions associated with fetal heart rate (FHR) decelerations (Murakami *et al.*, 1985; Fairlie *et al.*, 1989; Weiss *et al.*, 1991; Sakai *et al.*, 1997; Tadmor *et al.*, 1999; Li *et al.*, 2003).

Regardless of the upstream mechanism, studies using near-infrared spectroscopy and pulse oximetry confirm that both first and second stage uterine contractions are associated with reduced fetal oxygenation, which recovers after the end of the contraction (Peebles *et al.*, 1992; McNamara & Johnson, 1995). In the vast majority of labours, these brief periods of impaired gaseous exchange are well tolerated by the healthy fetus. This is partly due to the restoration of placental function between contractions, which is normally sufficient to largely reverse hypoxaemia, hypercapnia and metabolic acidaemia. Nevertheless, this repeated impairment of gaseous exchange leads to a small, but consistent reduction in pH, pO_2 and an increase in lactate and pCO_2 in normal, uncomplicated labour (Modanlou *et al.*, 1974; Huch *et al.*, 1977; Kro *et al.*, 2010). In contrast, both spontaneous and oxytocin-induced uterine hyperstimulation are associated with increased risk of fetal acidaemia (Bakker *et al.*, 2007) and a persistent reduction in fetal cerebral oxygenation (Klink *et al.*, 1981; Johnson *et al.*, 1994; Peebles *et al.*, 1994; Simpson & James, 2008).

The defining characteristic of labour is therefore brief, but repeated, periods of fetal hypoxaemia. It is important to appreciate that this intermittent contraction-related hypoxaemia can be superimposed on pre-existing mild-moderate hypoxaemia associated with antenatal placental insufficiency (for example in the setting of fetal growth restriction) (Morrison, 2008; Brain *et al.*, 2015; Chauhan *et al.*, 2017). Acute severe hypoxaemia can also occur during labour due to complications such as placental abruption, uterine rupture or cord prolapse. Although sentinel events are associated with a high risk of hypoxic-ischaemic injury in their own right (Westgate *et al.*, 1999b; Martinez-Biarge *et al.*, 2012), they contribute about 25% of cases of hypoxic-ischaemic encephalopathy (Westgate *et al.*, 1999b; West *et al.*, 2005; Jonsson *et al.*, 2014). Thus we must appreciate that even in the absence of sentinel events, all labours are still associated with intermittent fetal hypoxaemia.

The fetus has impressive adaptations to defend itself against all of these patterns of hypoxaemia (Giussani, 2016; Bennet *et al.*, 2017). One of the earliest advances was the realisation that the fetus is adapted to live with exceptionally low partial pressures of oxygen, leading to the phrase *"Everest in utero"* (Barcroft, 1946). This is in part made possible due to the structure of fetal haemoglobin, high basal blood flow and unique vascular shunts which promote preferential streaming of highly oxygenated blood towards critical organs including the heart and brain (Rudolph, 1985; Kiserud *et al.*, 2000; Harding & Bocking, 2001). Critically, the healthy fetus has an impressive anaerobic reserve. This is primarily determined by the exceptionally high levels of myocardial glycogen, which is tightly linked to the ability to maintain cardiovascular function during severe hypoxaemia (Dawes *et al.*, 1959; Shelley, 1961). Other organs including the brain are inherently resistant to hypoxic injury, partly by suppressing metabolism (Drury *et al.*, 2012). These basal adaptations are coupled with active defences to further prioritise blood supply and reduce oxygen consumption during acute hypoxaemia. Classical studies used fetal sheep to finely dissect the physiology of fetal adaptations to both prolonged mild-moderate hypoxaemia and acute severe hypoxaemia as reviewed (Giussani, 2016; Bennet, 2017). These influential studies showed that the fetus primarily adapts to sustained periods of hypoxaemia with an initial neural reflex but this is quickly augmented and replaced by non-neural, humoral mechanisms (Giussani, 2016; Bennet, 2017).

It is important to appreciate that such prolonged periods of hypoxaemia are not consistent with the typical pattern of intermittent hypoxaemia associated with labour, and may have inadvertently contributed to a misunderstanding of how the fetus successfully adapts to labour. The impairment of gaseous exchange related to uterine contractions is well appreciated clinically (Ayres-de-Campos & Arulkumaran, 2015). Unfortunately a long-standing belief that the majority of FHR decelerations during labour are triggered by non-hypoxic events (Hon & Quilligan, 1967; Ayres-de-Campos *et al.*, 2015) has de-emphasised the importance of repeated fetal hypoxaemia. In contrast, modern evidence supports that the vast majority of FHR decelerations are triggered by hypoxaemia and represent the fetus's protective adaptation against hypoxaemia (the peripheral chemoreflex) (Lear *et al.*, 2016b). Understanding the fetal adaptations to brief, but repeated hypoxaemia is therefore critical to understanding how the great majority of fetuses survive labour without compromise, in what situations these adaptations are insufficient, and critically how these adaptations are reflected on the intrapartum FHR trace – the gold standard for assessing fetal wellbeing during labour. This review will therefore focus on the fetal cardiovascular adaptations to intermittent hypoxaemia. In contrast to a reliance on humoral factors during prolonged hypoxaemia, the fetal adaptation to intermittent hypoxaemia is predominantly mediated by repeated activation of the peripheral chemoreflex leading to repeated, intense activation of both arms of the autonomic nervous system.

The peripheral chemoreflex – the rapid adaptation to hypoxaemia

The fetus responds to hypoxaemia with coordinated cardiovascular, neurophysiological and behavioural adaptations (Giussani, 2016; Bennet, 2017). The peripheral chemoreflex mediates the immediate, rapid responses to hypoxaemia. It triggers an increase in parasympathetic activity causing a rapid FHR deceleration (Itskovitz *et al.*, 1983; Giussani *et al.*, 1993), reducing combined ventricular output (CVO). This reduction in CVO is primarily related to the reduction in FHR as indices of preload have consistently been shown to be stable, or even increased, during graded reductions in umbilical blood flow (Edelstone *et al.*, 1980; Itskovitz *et al.*, 1987). This presumptively reduces myocardial oxygen consumption. The peripheral chemoreflex actively accommodates the fall in CVO by simultaneously increasing sympathetic nervous activity (Jensen & Lang, 1992; Giussani *et al.*, 1993). This promotes rapid, intense peripheral vasoconstriction (Figure 1), resulting in hypertension and centralisation of (the now reduced) CVO to key organs such as the brain, heart and adrenal glands (Jensen *et al.*, 1987; Jensen & Lang, 1992; Giussani *et al.*, 1993). The vasoconstrictor effects of sympathetic neural activation are supplemented by release of humoral factors including adrenal catecholamines, cortisol, angiotensin, vasopressin and neuropeptide Y (Broughton *et al.*, 1974; Jones & Robinson, 1975; Perez *et al.*, 1989; Giussani *et al.*, 1993; Giussani *et al.*, 1994a; Giussani *et al.*, 1994b; Fletcher *et al.*, 2000; Galinsky *et al.*, 2014).

The peripheral chemoreflex is highly tailored. Greater reductions in oxygen tensions (e.g. due to greater impairment of placental gaseous exchange) are associated with more intense activation and in turn deeper falls in fetal heart rate (decelerations). In healthy near-term fetal sheep, a 50% reduction in uteroplacental flow is needed to trigger a deceleration (Itskovitz *et al.*, 1983; Ross *et al.*, 2013). Maximal activation of the peripheral chemoreflex is observed when uteroplacental blood flow

is reduced to below 90% (Itskovitz *et al.*, 1983). Although it is currently not possible to continuously monitor peripheral vasoconstriction during labour, evidence of centralisation of blood flow has been observed in growth-restricted fetuses responding positively to an oxytocin challenge test (Li *et al.*, 2006) and during active labour in association with brief periods of fetal deoxygenation as assessed by pulse oximetry (Siristatidis *et al.*, 2004). The parasympathetic component of the peripheral chemoreflex is shown by repetitive FHR decelerations occurring with intrapartum uterine contractions (Lear *et al.*, 2016b). Thus, intrapartum decelerations simply indicate reflex responses to reduced uteroplacental gaseous exchange, while repeated deep decelerations indicate near abolition of gaseous exchange.

The peripheral chemoreflex is capable of repeated activation throughout labour

Most fetuses enter labour with a large reserve of placental capacity and myocardial glycogen stores that help to accommodate the repeated brief reductions in oxygen supply during contractions. When this is coupled with the impressive ability of the healthy fetus to mount protective adaptations against hypoxaemia, the vast majority of fetuses tolerate labour exceptionally well. This is understandably finite, and fetal compromise results when this tolerance is exceeded. In turn, uterine contraction strength, frequency and duration are the key factors that determine whether and how quickly fetuses will develop hypotension. The presence and severity of hypotension is critically associated with both reduced cerebral blood flow and ultimately with intrapartum hypoxic-ischaemic injury across different settings and experimental paradigms (Gunn *et al.*, 1992; Mallard *et al.*, 1994; de Haan *et al.*, 1997; Ikeda *et al.*, 1998; Fujii *et al.*, 2003). Thus, we may consider the development of hypotension as an empirical marker of fetal compromise.

Ultimately, the proportion of time the uterus spends at resting tone compared with contracting tone will determine the extent to which fetal gas exchange can be restored between contractions. Consistent with this, reduced relaxation time or increased contraction frequency is associated with persistent reductions in fetal oxygenation (Klink *et al.*, 1981; Johnson *et al.*, 1994; Peebles *et al.*, 1994; Simpson & James, 2008), an increased risk of fetal acidaemia (Bakker *et al.*, 2007) and in turn an increased risk of intrapartum decelerations (Stewart *et al.*, 2012). Thus, interventions, which increase the frequency and/or duration of uterine contractions, place the fetus at a higher risk of compromise.

These clinical findings are strongly paralleled by studies in near-term fetal sheep, which provide insight into the mechanisms through which the fetus continues to adapt to repeated brief hypoxaemia. In these studies severe hypoxaemia was induced by brief, 1 minute, complete umbilical cord occlusions repeated every 5 or 2.5 minutes (consistent with early and active labour, respectively) (Westgate *et al.*, 1999a) or by 2 minute complete umbilical cord occlusions repeated every 5 minutes (Westgate *et al.*, 2001; Galinsky *et al.*, 2014). As explored next, these studies have collectively revealed that the peripheral chemoreflex is exceptionally robust, and able to be repetitively activated over many hours without becoming attenuated. Critically, even with limited

time for reperfusion between complete umbilical cord occlusions with progressive hypotension and acidaemia, the peripheral chemoreflex continues to be intensely activated with every episode of hypoxaemia. The peripheral chemoreflex therefore remains the guardian of fetal wellbeing in both cases of successful and unsuccessful adaptation to labour.

Cardiovascular changes in fetuses tolerating labour-like hypoxaemia

Studies in near-term fetal sheep have shown that the healthy fetus can tolerate even severe intermittent periods of hypoxaemia essentially indefinitely, providing that a sufficient period of reperfusion is allowed between periods of hypoxaemia. Fetal sheep effectively tolerated 1 minute complete umbilical cord occlusions repeated every 5 minutes (consistent with the contraction frequency during early labour) for 4 hours (a total of 49 occlusions) without any hypotension. These fetuses responded to all occlusions with an intense peripheral chemoreflex, including a rapid deep deceleration and hypertension (Figure 2) and only minimal acidaemia was observed at the end of the experiment (pH 7.34±0.03, base deficit 1.1±1.4 mmol/L, lactate 4.2±1.5 mmol/L) (Bennet *et al.*, 2005).

These findings illustrate two important points. Firstly, the peripheral chemoreflex is able to be reliably re-activated during repeated contractions over prolonged periods of time to effectively promote centralisation of blood flow and hypertension. In turn, this helps explain why the majority of babies are at no risk of hypotension and do not develop marked acidaemia despite showing repeated decelerations during labour – the healthy fetus given sufficient reperfusion between decelerations is well able to adapt to repeated hypoxaemia. The finding that fetuses showed only mild acidaemia is additionally important considering that they were subjected to a cumulative duration of 49 minutes of complete umbilical cord occlusion over 4 hours (Bennet *et al.*, 2005). This illustrates that the healthy placenta is able to rapidly reverse the effects of temporary impaired gaseous exchange, and that the fetus can rapidly metabolize lactate (directly or by conversion to glucose (Carter *et al.*, 1995; Bartelds *et al.*, 2000)), and therefore that the effect of uterine contractions on gaseous exchange and lactate will often not be apparent on umbilical blood gases.

Cardiovascular changes in fetuses failing to tolerate labour-like hypoxaemia

In contrast, fetuses exposed to repeated hypoxaemia with insufficient periods of reperfusion progressively develop hypotension during occlusions, severe acidaemia and eventually neural injury (de Haan *et al.*, 1997). Near-term fetal sheep exposed to 1 minute complete umbilical occlusions repeated every 2.5 minutes (consistent with active labour) until severe hypotension developed (76.5±21.2 occlusions, or an average 3.2 hours of occlusions) responded to the first three cord occlusions with deep decelerations and sustained hypertension during occlusions. From the fourth occlusion onwards, fetuses showed a biphasic arterial pressure response consisting of initial hypertension followed by a fall in blood pressure during the occlusion, before recovering to or above baseline between occlusions (Westgate *et al.*, 1999a; Bennet *et al.*, 2005). The fall in arterial pressure became more rapid and severe with continued occlusions, progressively leading to severe hypotension during occlusions (nadir of 15.5±3.0 mmHg during the final occlusion). Severe acidaemia progressively developed with successive occlusions (pH 6.92±0.04, base deficit 19.7±1.8 mmol/L, lactate 14.8±1.2 mmol/L after the final occlusion) (Bennet *et al.*, 2005).

Mechanisms of evolving hypotension

There is now good evidence that the development of intermittent hypotension during brief repeated umbilical cord occlusions is not due to failure to mount an effective peripheral chemoreflex. Fetal sheep exposed to 2 minute complete umbilical cord occlusions repeated every 5 minutes until severe hypotension developed (18.7±2.3 occlusions) responded to all occlusion with rapid peripheral vasoconstriction intense enough to reduce femoral blood flow essentially to zero (Galinsky *et al.*, 2014). Strikingly, this intense peripheral vasoconstriction was observed even in the final occlusions of the experiment when all fetuses were simultaneously developing severe, rapid hypotension and despite severe acidaemia (pH 6.99±0.03, lactate 12.5±0.8 mmol/L) (Galinsky *et al.*, 2014). In contrast, chemically sympathectomized fetuses showed impaired and delayed peripheral vasoconstriction during repeated umbilical cord occlusions leading to more rapid onset hypotension (Galinsky *et al.*, 2014). This finding illustrates that the sympathetic nervous system continues to be intensely activated during severe repeated hypoxaemia, even in the face of severe fetal hypotension.

The parasympathetic arm of the peripheral chemoreflex appears to be equally robust. In near-term fetal sheep exposed to 1 minute complete umbilical cord occlusion repeated every 2.5 minutes until severe hypotension developed, the initial parasympathetic-mediated deceleration became more rapid as fetuses became acidemic and hypotensive during occlusions (Bennet *et al.*, 2005). The parasympathetic response to repeated hypoxaemia is therefore not only sustained, but augmented during progressive fetal compromise. Metabolic acidosis may have contributed to this, as previous evidence in near-term fetal sheep has shown that infusion of acidified saline to induce mild acidosis was associated with a greater fall in FHR and increased peripheral vasoconstriction during moderate hypoxaemia (Thakor & Giussani, 2009). Once the initial fall in FHR is achieved, FHR is regulated by a balance between continued parasympathetic activity and the positive chronotropic effects of adrenal catecholamines, acting through beta-adrenergic receptors (Galinsky *et al.*, 2016). This can result in a partial recovery in FHR despite continuing cord occlusion, especially in fetuses tolerating hypoxaemia well (Giussani *et al.*, 1993; Galinsky *et al.*, 2016). In contrast, the nadir of decelerations progressively deepens with evolving fetal compromise and hypotension (Bennet *et al.*, 2005). Given that adrenaline and noradrenaline levels remain extremely high during fetal compromise (Galinsky *et al.*, 2014), deepening decelerations presumptively represent impaired myocardial responsiveness and contractility, potentially due to a combination of intracellular acidosis, depletion of myocardial glycogen and evolving myocardial injury (Dawes *et al.*, 1959; Shelley, 1961; Gunn *et al.*, 2000).

Although these studies demonstrate that the peripheral chemoreflex can be continually activated at the start of labour-like hypoxaemia for many hours, we know less about how long autonomic tone is maintained during each individual period of deep hypoxaemia. During studies of single periods of prolonged hypoxaemia, the peripheral chemoreflex becomes attenuated after approximately 90 seconds (Barcroft, 1946). The finding that intense peripheral vasoconstriction was maintained during brief 2 minute complete umbilical cord occlusions despite severe hypotension suggests that overall combined sympathetic tone (i.e. neural and adrenal) is sustained even longer (Galinsky *et al.*, 2014).

However, there is indirect evidence that parasympathetic tone during repeated labour-like hypoxaemia becomes shorter-lived with progressive fetal compromise.

Systematic studies in fetal sheep have shown that overshoot tachycardia occurring immediately after a deceleration is mediated by the combination of loss of parasympathetic tone and β-adrenergic stimulation (Galinsky *et al.*, 2016). Overshoot tachycardia is always seen after 2 minute complete umbilical cord occlusions, confirming that parasympathetic tone is lost by 2 minutes of severe hypoxaemia (Westgate *et al.*, 2001; Galinsky *et al.*, 2016; Lear *et al.*, 2016a), consistent with studies of parasympathetic blockade (Barcroft, 1946). In contrast, in fetal sheep, overshoot did not occur after 1 minute complete umbilical cord occlusions repeated every 2.5 minutes, until hypotension began to develop (Westgate *et al.*, 2001). This infers that the parasympathetic tone became attenuated earlier during hypoxaemia after the onset of hypotension. The mechanism is unknown, but speculatively may reflect direct neural inhibition due to impaired perfusion of the brainstem (Jensen *et al.*, 1999).

Nevertheless, it is important to appreciate that even if autonomic tone is lost during individual periods of hypoxaemia, both arms of the autonomic nervous system rapidly recover with even brief reperfusion, allowing the peripheral chemoreflex to be reactivated (Figures 1 and 3) (Bennet *et al.*, 2005; Galinsky *et al.*, 2014). This may be partly related to the consistent finding in the above studies that arterial pressure rapidly recovers to above baseline levels between occlusions, even after the onset of severe hypotension during occlusions (Bennet *et al.*, 2005; Westgate *et al.*, 2005; Wassink *et al.*, 2013; Galinsky *et al.*, 2014). This likely allows rapid restoration of brainstem perfusion and substrate supply, and recovery of the autonomic centres.

Overall, these studies confirm that the healthy fetus has an impressive tolerance to repeated hypoxaemia. However, even a healthy fetus with normal placental function may be unable to prevent hypotension during tonic contractions or uterine hyperstimulation, as may occur for example, with oxytocin and prostaglandin for induction or augmentation of labour (Winkler & Rath, 1999). When progressive fetal decompensation during labour occurs, it is not related to the failure of autonomic adaptation, but to inability to maintain CVO during hypoxaemia. Given that adrenaline and noradrenaline levels remain extremely high during fetal compromise (Galinsky *et al.*, 2014), this strongly denotes that responsiveness to β-adrenergic stimulation becomes impaired (Bennet *et al.*, 2005). This is likely due to a combination of exhaustion of myocardial glycogen and evolving reversible cardiac injury leading to impaired contractility (Dawes *et al.*, 1959; Shelley, 1961; Gunn *et al.*, 2000). Consistent with a role for cardiac injury in humans, neonatal hypoxic-ischaemic encephalopathy is highly associated with increased plasma troponin-T levels (Jones *et al.*, 2017).

Does prior hypoxaemia attenuate the peripheral chemoreflex?

There is some evidence in fetal sheep that the peripheral chemoreflex may become attenuated by repeated moderate hypoxaemia (Giussani *et al.*, 1997; Green *et al.*, 2001). Giussani and colleagues found that during a series of partial umbilical cord occlusions for 5 minutes repeated 12 times with 15 minutes of reperfusion between occlusions, that FHR fell more slowly ("was attenuated") and that peripheral vasoconstriction during the final occlusion was reduced, after four hours of repeated

hypoxaemia (Giussani *et al.*, 1997). These studies could be taken to suggest that exposure to mild hypoxaemia either antenatally, or during early labour, could impair the fetal adaptation to more intense hypoxaemia during active labour. However, it is important to appreciate that this paradigm is much more prolonged, less frequent and milder than typical hypoxaemia during labour, and critically did not result in acidaemia or hypotension. It is therefore reasonable to suggest that these findings likely reflect effective adaptation through humoral mechanisms to a non-life threatening insult. More recent studies suggest that peripheral chemoreflex activation becomes progressively more intense and even more rapid during labour-like hypoxaemia and progressive acidosis/hypotension (Bennet *et al.*, 2005; Ross *et al.*, 2013). The finding of attenuated responses in the studies of mild hypoxaemia reinforces the concept that the peripheral chemoreflex is a tailored response, with reduced responses observed when fetal survival is not threatened but augmented during greater homeostatic challenges. This therefore fulfils a need to balance conservation of oxygen against the need to allow peripheral perfusion and oxygen consuming behaviour/development.

The importance of prelabour placental function and anaerobic reserve

The above studies were performed in healthy near-term fetal sheep. It is well known that fetal growth restriction is associated with high rates of perinatal complications (Chauhan *et al.*, 2017; Temming *et al.*, 2017). Near-term fetal sheep with spontaneous pre-existing hypoxaemia showed early onset of hypotension even during 1 minute complete umbilical cord occlusions repeated every 5 minutes (consistent with early labour) whereas normoxic fetal sheep were able to remain normotensive (Westgate *et al.*, 2005). The blood pressure response was likewise characterized by initial hypertension during occlusions at the start of the experiment and shifted to a biphasic pattern of initial hypertension followed by progressive hypotension during occlusions (Wassink *et al.*, 2013). The progressive development of severe acidaemia (pH 7.07±0.05, base deficit 14.5±1.7 mmol/L, lactate 9.3±2.2 mmol/L after the final occlusion) in these fetuses shows that despite 4 minutes of reperfusion, placental function was insufficient to reverse even a low frequency of impaired gaseous exchange (Westgate *et al.*, 2005; Wassink *et al.*, 2013). The specific mechanisms of the failure of these fetuses to tolerate low frequency occlusions compared to healthy fetal sheep are unclear, but likely reflects reduced reserves of myocardial glycogen (Shelley, 1961).

Perspectives and the search for effective biomarkers

It is often implied that hypoxaemia is only a significant factor in the minority of births associated with severe acidaemia and fetal compromise. This likely originates in the historical belief that most intrapartum decelerations do not reflect hypoxaemia (Lear *et al.*, 2016b). As reviewed here, hypoxaemia, or more correctly the fetal adaptation to repeated brief hypoxaemia, is the key feature regulating intrapartum FHR changes, including the vast majority of intrapartum decelerations. The ubiquitous nature of hypoxaemia during labour is balanced by the remarkable fetal tolerance and ability to mount coordinated adaptations against hypoxaemia. The recent studies highlighted in this review reveal that the peripheral chemoreflex remains an integral part of the fetal adaptation to labour-like hypoxaemia, even when fetuses are developing severe metabolic acidaemia and

hypotension with evolving neural injury (de Haan *et al.*, 1997; Wassink *et al.*, 2013). Because of these robust fetal adaptations, and the fact that injury only occurs in a narrow window between intact survival and death, identification of fetal hypoxaemia per se is not very useful in clinical practice.

There is therefore a critical need to identify new biomarkers to identify fetuses at risk of failing to tolerate labour. The simplest and most straightforward approach to improving the usefulness of current fetal heart rate monitoring is to appreciate the physiological significance of intrapartum decelerations. The focus of clinical training should be redirected to the depth, duration and frequency of intrapartum decelerations, rather than their timing. Supporting this, recent evidence from a large prospective cohort has highlighted that total deceleration area (i.e. taking into account the depth, duration and frequency of all decelerations) shows the best association with fetal acidaemia (Cahill *et al.*, 2018). Impressively, this study suggested that the sole use of total deceleration area would be associated with a number of caesareans needed-to-treat of five to prevent one case of acidaemia (Cahill *et al.*, 2018). This and similar studies have highlighted the superior clinical utility of assessing decelerations in a physiologically relevant manner, in contrast to the historical focus on timing (Cahill *et al.*, 2012b; Martí Gamboa *et al.*, 2016; Triebwasser *et al.*, 2016; Georgieva *et al.*, 2017). Future work should establish population-based thresholds of the burden or area of decelerations that the average healthy human fetus can tolerate during labour. This in turn must be balanced by the understanding that the tolerance of individual fetuses is highly variable and influenced by fetal anaerobic reserve and overall pre-labour health (Westgate *et al.*, 2005; Wassink *et al.*, 2013; Amaya *et al.*, 2016). There is additional need to better understand the implications of further factors, including antenatal glucocorticoid treatment and gestational age. Fetal sheep experiments have shown that dexamethasone and advancing gestational age affect the pattern and magnitude of FHR responses to moderate isocapnic hypoxaemia (Fletcher *et al.*, 2003; Jellyman *et al.*, 2005; Fletcher *et al.*, 2006). Further studies are needed to clarify the implications of these factors for severe repetitive labour-like hypoxaemia.

Clinical monitoring using total deceleration area will likely only allow stratification of risk. We propose that ideally deceleration area should be used in conjunction with additional biomarkers of fetal compromise. The “Holy Grail” would of course be a continuous measure of fetal arterial blood pressure or cerebral perfusion, but this is currently not feasible. Changes in FHRV, baseline FHR, and additional measures such as ST segment changes can offer information on fetal wellbeing. However, decades of clinical and preclinical work leads to the conclusion that these are only partially effective as biomarkers of fetal compromise (Westgate *et al.*, 2007; Cahill *et al.*, 2012a; Lear *et al.*, 2016b; Cahill *et al.*, 2018). Considering the evidence discussed in this review that progressive hypotension and eventual cerebral hypoperfusion is primarily associated with impaired myocardial contractility rather than autonomic impairment, we propose that future searches for biomarkers should be specifically tailored towards markers of failing contractility, assessed during intrapartum decelerations in particular. Given that the current system of intrapartum FHR interpretation is heavily based on outdated physiological concepts, we propose that the first step is the physiologically correct understanding of the big picture – that intrapartum decelerations are a direct index of the fetal reflex responses to fetal hypoxaemia.

Additional information

Competing interests

The authors have no competing interests to declare.

Author contributions

C.A.L. and A.J.G. conceptualised this review. C.A.L. drafted the manuscript. C.A.L., G.W., J.A.W., J.G.N, A.U., R.G., L.B., and A.J.G. were involved in the critical review and revision of this manuscript. All authors listed qualify for authorship and approved the final version of this review.

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Figure legends

Abstract figure: The slippery slope during labour. Labour is naturally associated with repeated periods of impaired gaseous exchange and therefore intermittent hypoxaemia. The fetus responds by protective activation of the peripheral chemoreflex, to firstly reduce heart rate (intrapartum decelerations) in order to reduce myocardial oxygen usage, and to promote peripheral vasoconstriction to centralise blood flow to the heart, brain and adrenal glands. The healthy fetus is therefore at low risk of developing hypotension thanks to these robust defences. This tolerance is nonetheless finite, and prolonged severe hypoxaemia depletes fetal anaerobic reserves (primarily

related to myocardial glycogen levels), resulting in progressive loss of myocardial contractility. Despite continued peripheral chemoreflex activation and effective peripheral vasoconstriction, reduced combined ventricular output results in evolving hypotension. Hypotension and subsequent cerebral hypoperfusion is the critical element that leads to hypoxic-ischaemic brain injury. pO_2, partial pressure of oxygen.

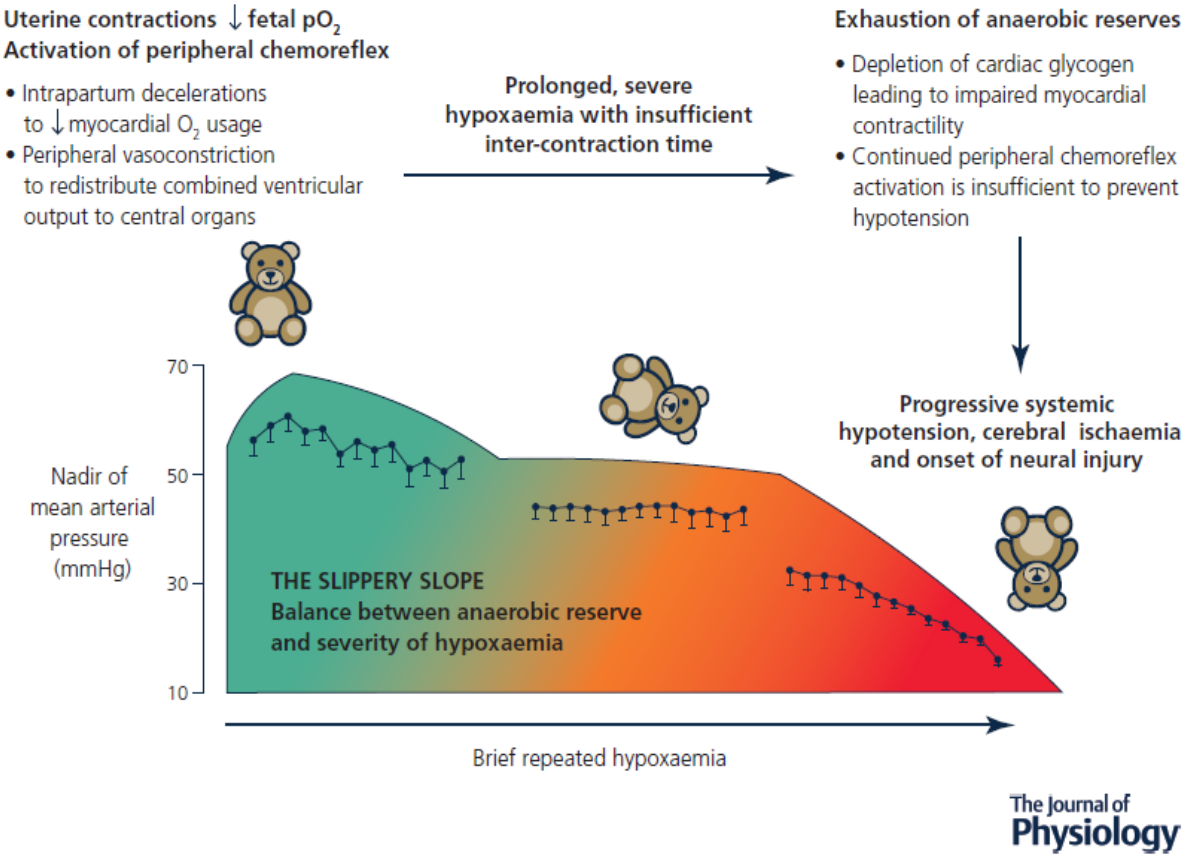


Figure 1: Peripheral chemoreflex activation during labour. The peripheral chemoreflex is the protective fetal response to acute hypoxaemia caused by intrapartum uterine contractions. Its activation results in a reflex increase in parasympathetic activity, to trigger intrapartum decelerations, and an increase in sympathetic nervous activity, to promote peripheral

vasoconstriction and centralisation of blood flow to the heart, brain and adrenal glands. The severity/duration of hypoxaemia during labour is typically brief, meaning that autonomic activity is sustained throughout contractions. However, even if autonomic activity is lost during individual contractions, it rapidly recovers with reperfusion The peripheral chemoreflex can be continually activated throughout labour, even in the face of evolving fetal compromise. P_aO_2, arterial partial pressure of oxygen.

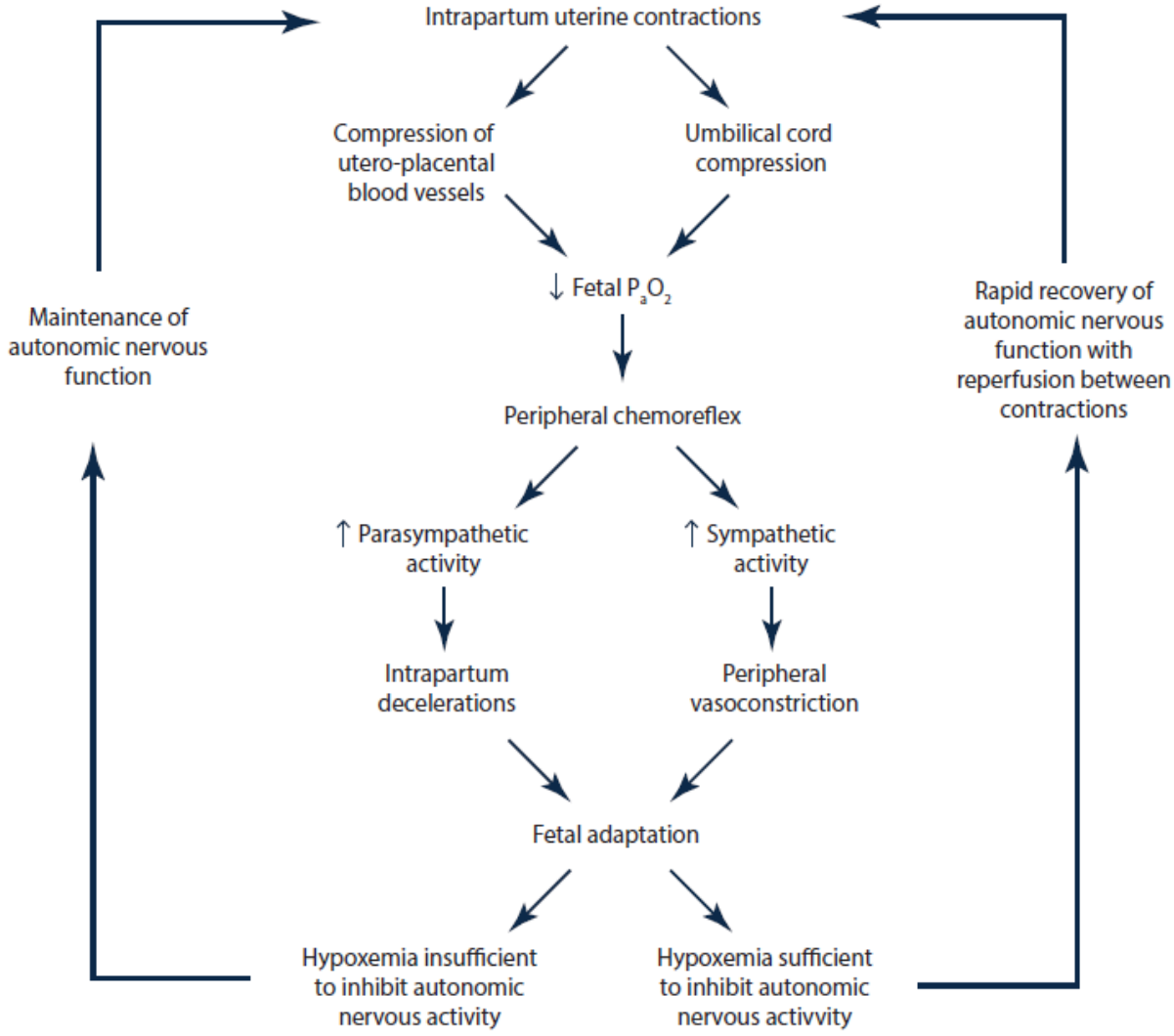


Figure 2: Cardiovascular changes in fetuses tolerating labour-like hypoxaemia. Fetal heart rate (FHR, solid lines) and mean arterial pressure (MAP, dashed lines) in near-term fetal sheep during 1 minute complete umbilical cord occlusion (UCO) repeated every 5 minutes (n = 8) for 4 hours (total

of 49 UCOs). The top panel shows the second UCO, the middle panel shows the middle UCO and the bottom panel shows the penultimate UCO. Fetuses effectively adapted to this severity and frequency of UCO. Each occlusion was associated with a rapid deceleration and sustained hypertension, mediated by peripheral chemoreflex activation. Hypotension was never observed in these fetuses. Data are 1 second means±SEM (shown as dotted lines). The periods of umbilical cord occlusion are shown in grey. Base deficit (BD) and lactate values are given in mmol/L. Figure modified from (Bennet *et al.*, 2005).

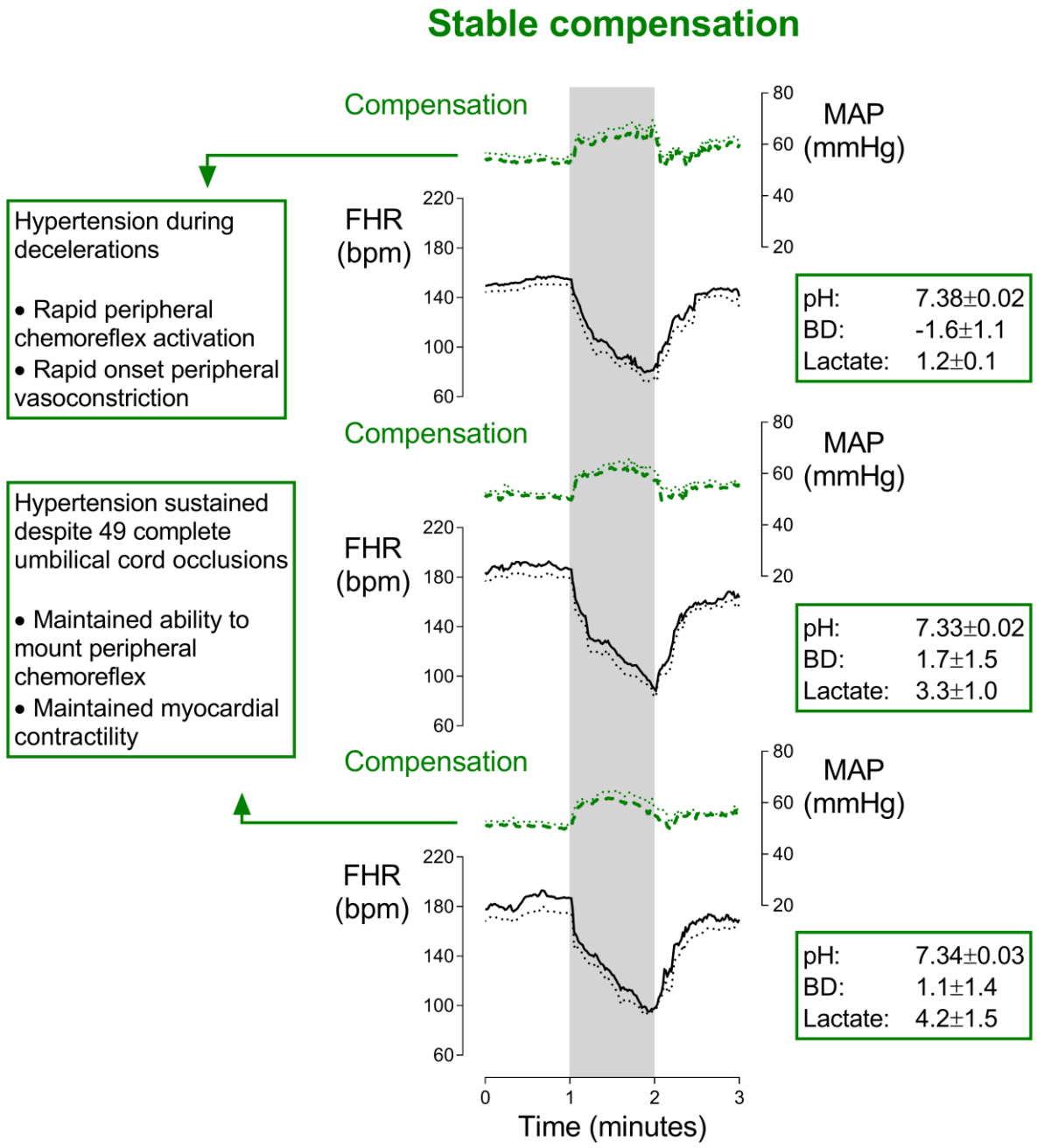
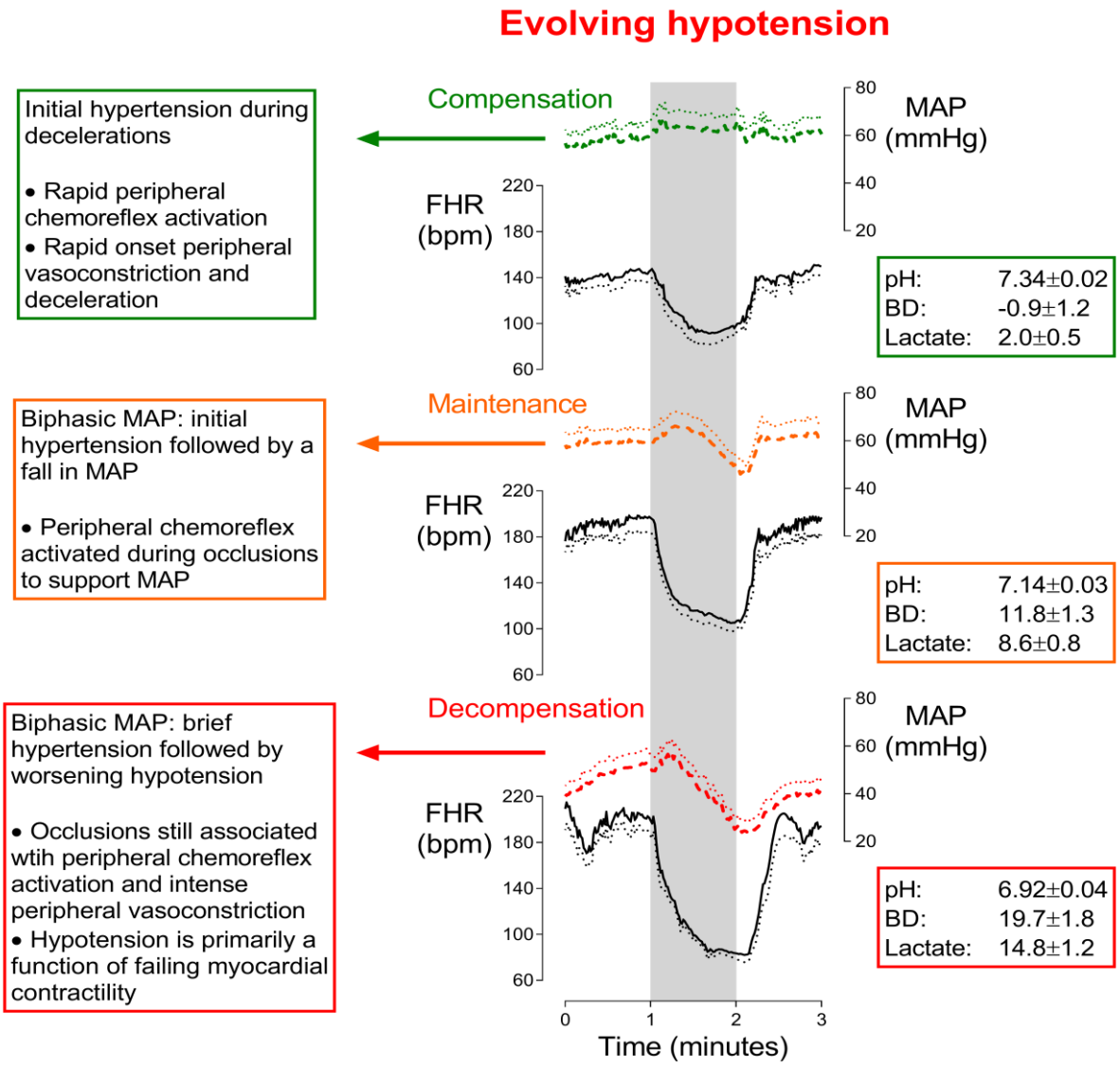


Figure 3: Cardiovascular changes in fetuses failing to tolerate labour-like hypoxaemia. Fetal heart rate (FHR, solid lines) and mean arterial pressure (MAP, dashed lines) in near-term fetal sheep during 1 minute complete umbilical cord occlusion (UCO) repeated every 2.5 minutes (n = 8) until severe hypotension developed (76.5±21.2 UCOs). The top panel shows the second UCO, the middle panel shows the middle UCO and the bottom panel shows the penultimate UCO. Fetuses initially tolerated this frequency and severity of UCOs, displaying hypertension and rapid decelerations during UCOs. The arterial pressure response progressively became biphasic as fetal tolerance was overcome, with initial hypertension followed by a fall in arterial pressure during occlusion. Fetal decompensation was associated with short lived hypertension and marked hypotension during occlusion. The associated decelerations became progressively deeper with the onset of hypotension. Data are 1 second means±SEM (shown as dotted lines). The periods of umbilical cord occlusion are shown in grey. Base deficit (BD) and lactate values are given in mmol/L. Figure modified from (Bennet *et al.*, 2005).



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