

TOPICAL REVIEW

The myths and physiology surrounding intrapartum decelerations: the critical role of the peripheral chemoreflex

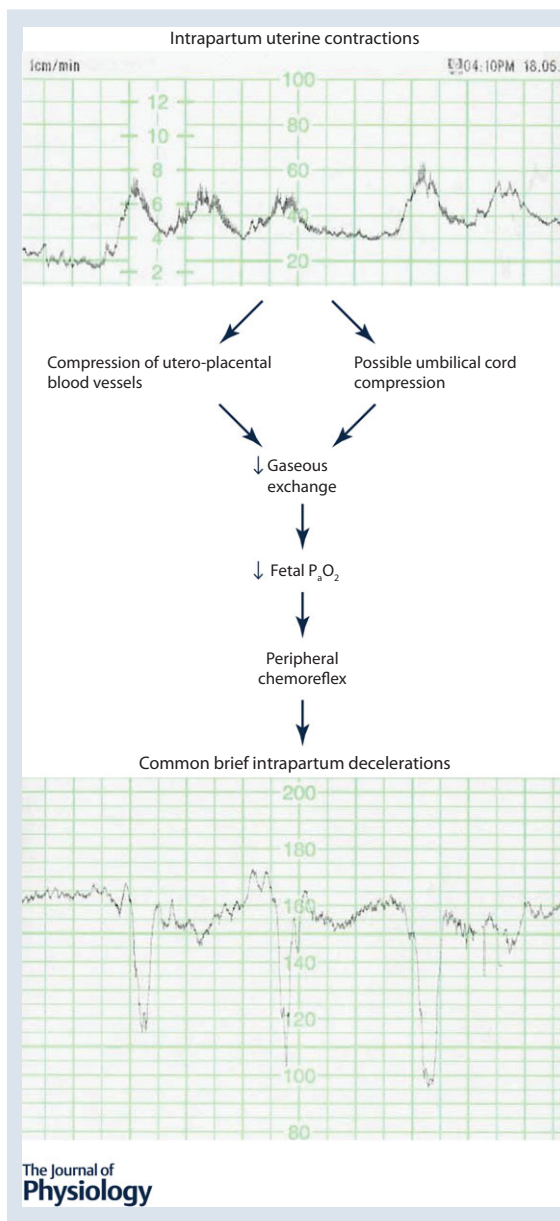
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Abstract A distinctive pattern of recurrent rapid falls in fetal heart rate, called decelerations, are commonly associated with uterine contractions during labour. These brief decelerations are mediated by vagal activation. The reflex triggering this vagal response has been variably attributed to a mechanoreceptor response to fetal head compression, to baroreflex activation following increased blood pressure during umbilical cord compression, and/or a Bezold–Jarisch reflex response to reduced venous return from the placenta. Although these complex explanations are still widespread today, there is no consistent evidence that they are common during labour. Instead, the only mechanism that has been systematically investigated, proven to be reliably active during labour and, crucially, capable of producing rapid decelerations is the peripheral chemoreflex. The peripheral chemoreflex is triggered by transient periods of asphyxia that are a normal phenomenon associated with all uterine contractions. This should not cause concern as the healthy fetus has a remarkable ability to adapt to these repeated but short periods of asphyxia. This means that the healthy fetus is typically not at risk of hypotension and injury during uncomplicated labour even during repeated brief decelerations. The physiologically incorrect theories surrounding decelerations that ignore the natural occurrence of repeated asphyxia probably gained widespread support to help explain why many babies are born

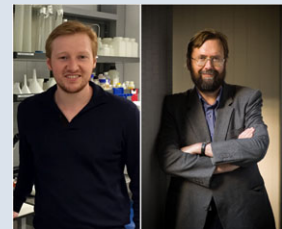
healthy despite repeated decelerations during labour. We propose that a unified and physiological understanding of intrapartum decelerations that accepts the true nature of labour is critical to improve interpretation of intrapartum fetal heart rate patterns.

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Abstract figure legend **The critical role of the peripheral chemoreflex in intrapartum decelerations.** Intrapartum uterine contractions are associated with an impairment of gaseous exchange, leading to transient fetal hypoxia and a rapid peripheral chemoreflex-mediated deceleration. This is the mechanism underpinning the vast majority of intrapartum decelerations. In contrast, it is commonly believed that intrapartum decelerations are instead largely due to baroreflex or Bezold–Jarisch reflex activation or alternatively to fetal head compression triggering a mechanoreflex-mediated deceleration. There is no evidence that any of these reflexes, other than the peripheral chemoreflex, commonly mediate intrapartum decelerations.

Christopher Lear is a PhD student working with Professors Alistair Gunn and Laura Bennet. His goal is to understand why some fetuses survive oxygen deprivation and infection and grow up to be completely normal, whereas others suffer injury or die after apparently identical exposure. His studies have highlighted both the extraordinary physiological resilience of the unborn child and the critical importance of understanding the physiological mechanisms of the fetal responses to major homeostatic challenges. **Alistair Jan Gunn** is a paediatrician-scientist who has conducted groundbreaking 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.



Introduction

Fetal heart rate (FHR) recordings are the only non-invasive tool that we have to continuously monitor the wellbeing of fetuses during labour. Recordings are most commonly derived from a Doppler ultrasound transducer on the maternal abdomen that measures the contractions of the fetal heart. Alternatively the fetal electrocardiogram can be recorded from an electrode attached directly to the fetal scalp. During labour, the clinician will assess all aspects of the FHR trace, including baseline FHR, FHR variability and the presence of accelerations and decelerations of FHR. Uterine contractions are recorded alongside the FHR trace and thus the FHR features are interpreted in relation to uterine activity to provide a broad, composite indication of fetal wellbeing. Many of these aspects, and the overall interpretation of intrapartum FHR traces have been discussed in detail elsewhere (Parer & Ikeda, 2007; Westgate *et al.* 2007; Lear *et al.* 2016) and are beyond the scope of this review.

The most contentious aspect of FHR monitoring is the significance of the rapid but brief falls in FHR, called decelerations, which almost always occur in association with uterine contractions. It is unequivocally established that these decelerations are mediated by vagal activation, and can be blocked by atropine in both humans (Mendez-Bauer *et al.* 1963; Caldeyro-Barcia *et al.* 1966) and animals (Barcroft, 1946; Itskovitz *et al.*

1983b; Westgate *et al.* 2007). However, the specific reflex that mediates FHR decelerations has been surprisingly controversial. The central scientific and pragmatic clinical question is what, if anything, does a deceleration tell us about the condition of the unborn child?

Before we can assess the scientific evidence we must first address the vexed issue of the terminology used to describe FHR decelerations and commonly held clinical beliefs about causation. Although three categories of deceleration are described (early, late and variable), unfortunately the exact definitions of each type and their clinical significance have varied, both with time and geography. For example, from the 1970s to the 90s most standard British textbooks classified decelerations only on the basis of whether they started and finished within the time frame of (i.e. in time with) a contraction ('early' decelerations) or whether there was a lag-time between the onset of the contraction and the onset of the deceleration ('late' decelerations) (Sholapurkar, 2012). This classification was applied irrespective of the deceleration shape. Indeed one of the authors (J.A.W.) recalls being taught only about early and late decelerations when training in the 1980s and only discovered the category of variable decelerations (characterised by their rapid fall in FHR to nadir, and a variable timing relationship with contractions) when commencing a research project in 1990. Even more alarming in retrospect was the associated clinical teaching that early decelerations were always due to head

compression and thus were always innocuous whereas late decelerations were always due to fetal hypoxia.

Unfortunately, these clinical associations are still held (even if subconsciously) by many generations of obstetricians. Failure to consider the key variables, depth, duration and frequency of 'early' decelerations, has led to many tragic outcomes. There have been noble and useful attempts on both sides of the Atlantic to standardise both the descriptions of FHR decelerations and integrate these into advice on management of overall FHR changes since the late 1990s (Parer *et al.* 2009; Ugwumadu, 2014). The focus on variable decelerations, which historically were attributed to cord compression, is slowly catching on in the UK but is bemoaned by some (Sholapurkar, 2012). Unfortunately, differences in paper speed (1 cm min^{-1} in the UK, Australasia and much of Europe compared with 3 cm min^{-1} in North America) cause geography-related discrepancies in the appearance and, thus, the interpretation of early and late decelerations (Westgate *et al.* 2007). The non-obstetric reader may feel somewhat confused at this point and perhaps amazed that such a critical aspect of intrapartum obstetrics (and one which is responsible for high litigation costs; Williams & Arulkumaran, 2004) remains unresolved.

There is now a wealth of experimental evidence, some old, some new, exploring the causes of FHR decelerations, which enable us both to evaluate commonly held clinical associations and provide an updated scientific basis for understanding decelerations. In contrast to the historically proposed 'origins' of decelerations, in this review we argue that the common, brief decelerations in labour are simply peripheral chemoreflex responses to transient but repeated asphyxia.

Are FHR decelerations due to fetal head compression?

During labour the fetal head presses on the uterine wall, leading to increased pressure on the skull, as measured with a strain gauge (Schwarcz *et al.* 1969). Pressure on the head increases further in the second stage of labour as the head is engaged in the birth canal, and after rupture of the chorio-amniotic membranes. Not long after the introduction of obstetric auscultation, this pressure on the fetal head was suggested to result in a slowing of the fetal heart rate (variably attributed to Kennedy, 1833 or Naegele, 1839). More recently, it has been further suggested that early decelerations, which often roughly parallel the increase in uterine tone, are consistently the result of this increased intracranial pressure and trigger a non-hypoxic reflex deceleration (Hon, 1958; Chung & Hon, 1959; Hon & Quilligan, 1968; Ott, 1976; Ball & Parer, 1992; Sholapurkar, 2012; Nageotte, 2015).

The neural pathways controlling such a reflex have never been described. Intuitively, they might be initiated by local pressure receptors in the scalp. However, if

head compression was a consistent trigger of early decelerations we might reasonably expect all fetuses to show decelerations either as soon as their head became engaged in the birth canal or during the second stage of labour, as the head descends through the vagina. This is not the case. Clinically, decelerations can equally occur or not occur during all stages of labour (Hon & Quilligan, 1967).

Next, we address studies showing that head compression can (if inconsistently; Chung & Hon, 1959) cause decelerations, but that this is only observed if the compression is severe enough to impair cerebral blood flow – hardly a benign event. It is questionable whether such severe increases in intracranial pressure are common during unobstructed labour. In fetal sheep, when intracranial pressure was increased through intracerebroventricular infusions to a level where systemic hypertension was induced but cerebral blood flow was maintained, decelerations were not observed (Harris *et al.* 1989). In a clinical study, manual pressure on the maternal abdomen over the fetal head variably provoked either decelerations or tachycardia (Walker *et al.* 1973). The inconsistent FHR response to head compression may be partly related to which particular area of the head is compressed (Chung & Hon, 1959). Additionally, it has been reported that pressure over the inferior aspect of the uterus often produced decelerations with slow resolution (Walker *et al.* 1973). This suggests that the rapid resolution of increased intracranial pressure is not sufficient to restore heart rate, and that slow recovery was more likely to reflect recovery from frank cerebral ischaemia (Walker *et al.* 1973).

Strongly supporting these data, manual head compression in full term fetal sheep was associated with decelerations and an accompanying 50% reduction in carotid blood flow (Paul *et al.* 1964). Highly consistent with the clinical observations of Walker and colleagues noted above, FHR took 10–30 s to recover after release of compression, in parallel with delayed recovery of carotid blood flow. This observation strongly suggests that decelerations were secondary to central nervous system hypoxia (Paul *et al.* 1964). Similarly, head compression in fetal sheep with a modified rib retractor was only associated with decelerations in 37% of cases. When a deceleration did occur, it was again associated with reduced cerebral blood flow and profound suppression of fetal electroencephalographic activity (Mann *et al.* 1972).

In summary, direct fetal head compression inconsistently causes decelerations and so is very unlikely to be a major contributor to intrapartum decelerations during the majority of labours. The findings discussed in this section illustrate that when fetal head compression does lead to a deceleration, the phenomenon is highly consistent with a Cushing response; a near-terminal response to reduced cerebral blood flow secondary to

increased intracranial pressure (Fodstad *et al.* 2006). Thus, if decelerations due to head compression do occur, for example during obstructed labour when the fetal head is engaged in the birth canal, these data suggest that such decelerations reflect severe cerebral hypoperfusion and hypoxia (Schiffrin *et al.* 2016), and in contrast with current proposed interpretation (Sholapurkar, 2012; National Institute for Health and Care Excellence, 2014), should not be considered to be benign.

Are FHR decelerations mediated by the baroreflex?

Others have proposed that the rapid variable decelerations (the category that constitutes the vast majority of intrapartum decelerations) could be a reflex response to the abrupt changes in blood volume and arterial blood pressure secondary to compression of the umbilical cord (Lee *et al.* 1975; Ott, 1976; Ball & Parer, 1992; Nageotte, 2015; Pinas & Chandrabaran, 2016). Partial compression of both the placenta and umbilical vein during contractions may initially promote transfer of blood to the fetus, increasing blood volume and thus blood pressure. With a further increase in contraction strength, both the umbilical vein and arteries become completely occluded, increasing total peripheral resistance of the fetus. Both of these events could increase fetal arterial blood pressure, and hypothetically trigger a baroreflex-mediated deceleration. As the contraction resolves and the umbilical arteries are unoccluded, peripheral resistance would be lost, with a reciprocal fall in fetal blood pressure and reduction in baroreflex activity (Ball & Parer, 1992; Sunderström *et al.* 2000; Gibbs & Arulkumaran, 2007; Hendler & Seidman, 2009).

Again, there is strikingly little evidence to support this concept. Umbilical cord compression can occur in labour, for example, during entanglements of the cord or cord prolapse, albeit there is no empirical evidence that it is the predominant cause of FHR decelerations in the majority of labours. Nonetheless, we can test this hypothesis by experimental occlusion of the umbilical cord. First, partial occlusion of the umbilical cord allows the effect of umbilical vein compression (or veins, since sheep have two umbilical veins) to be investigated. In near-term fetal sheep, FHR fell once umbilical blood flow was reduced by 50% or more (Itskovitz *et al.* 1983*b*). Despite this, two separate studies found no significant changes in arterial pressure, and thus the baroreflex cannot have been triggered during partial occlusion of the umbilical cord (Itskovitz *et al.* 1983*b*; Giussani *et al.* 1997).

In contrast to partial occlusion, rapid complete occlusion of the umbilical cord is associated with two separate increases in fetal arterial pressure, as seen in Figs 1 and 2. The first small increase occurs immediately at the onset of occlusion, suggesting that it reflects mechanical removal of the low resistance placental vascular bed,

leading to a net increase in total peripheral resistance. This increase in arterial blood pressure, however, is fleeting and small, well within normal baseline fluctuations in blood pressure. Thus, it is highly improbable that this first increase in blood pressure is sufficient to trigger a baroreflex.

Supporting this interpretation, Fig. 3 (left panels), shows a spontaneous contraction in a near-term fetal sheep that was associated with a rapid deep deceleration despite an initial fall in arterial pressure at the onset of deceleration. These data show that hypertension is not necessary to cause spontaneous decelerations. Indeed, only one of the decelerations shown in Fig. 3 was associated with an increase in mean arterial pressure at the start of the deceleration.

Next, as shown in Fig. 1 and multiple previous studies, the second, much larger and more sustained, rise in pressure occurs *after* the onset of the fall in FHR and takes

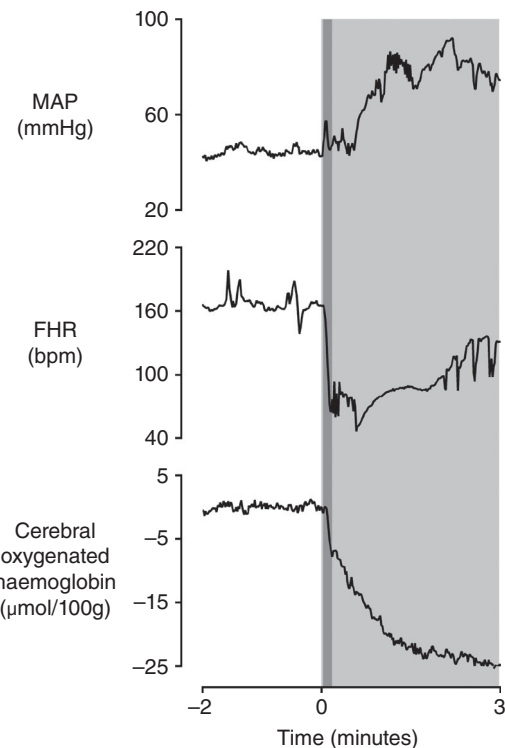


Figure 1. Relationship between mean arterial pressure (MAP, mmHg), fetal heart rate (FHR, beats min^{-1} (bpm)) and changes in cerebral oxygenated haemoglobin ($\mu\text{mol} (100 \text{ g})^{-1}$), as measured by near-infrared spectroscopy, during a prolonged complete umbilical cord occlusion in a near-term fetal sheep (0.85 of gestation)

The period of occlusion is shown in light grey. The overlapping dark grey area represents the initial and most rapid portion of the deceleration. Note how both FHR and cerebral oxygenated haemoglobin begin to fall in parallel at 6 s after the start of occlusion when MAP is not markedly higher than baseline. Data are 1 s averages. Cerebral oxygenated haemoglobin is shown relative to the average of the 2 min baseline period.

between 2 and 3 min to develop fully (Itskovitz *et al.* 1983b; Bennet *et al.* 2005; Booth *et al.* 2012). Given the time taken for this increase in pressure, it cannot possibly contribute to the initial fall in FHR and, importantly, may not develop fully during shorter periods of umbilical cord occlusion (Fig. 2). Critically, this second large increase in pressure is actively mediated by increased sympathetic nervous system (SNS) activity leading to fetal peripheral vasoconstriction (Itskovitz *et al.* 1983b; Giussani *et al.* 1993; Galinsky *et al.* 2014). In contrast, the baroreflex response is sympathoinhibitory and leads to peripheral vasodilatation (Charkoudian & Wallin, 2014), and so cannot explain the intense peripheral vasoconstriction during acute umbilical cord occlusion. This is highly consistent with early work by Lee and Hon in human fetuses, where decelerations were reported to occur after both partial and complete umbilical cord occlusion in association with either increased, decreased or no change in blood pressure. The authors concluded that the baroreflex could not be the common mechanism for decelerations (Lee & Hon, 1963).

Finally, the reader should also note preclinical evidence that the baroreflex is relatively immature before birth. In near-term fetal sheep, hypertension induced by phenylephrine did indeed result in a deceleration, but this was a very slow deceleration that took up to 30 s to develop fully (Booth *et al.* 2011). Phenylephrine-induced hypertension developed faster and was greater than

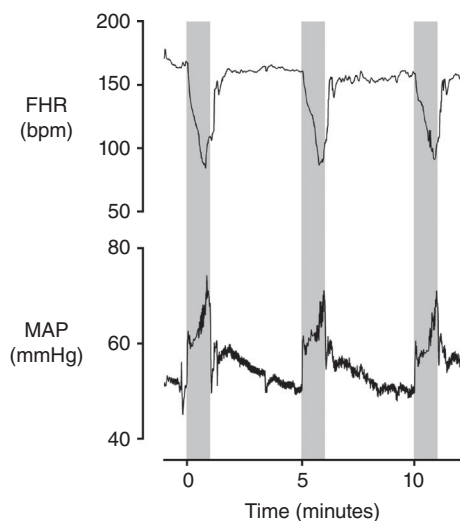


Figure 2. Fetal heart rate (FHR, beats min^{-1} (bpm)) and mean arterial pressure (MAP, mmHg) during three successive 1 min complete umbilical cord occlusions, repeated every 5 min in a near-term fetal sheep (0.85 of gestation)

The periods of occlusion are shown in grey. Note that the major actively mediated increase in MAP is delayed until after the onset of decelerations. Additionally the release of occlusion is not associated with the development of hypotension below baseline levels. The first occlusion shown here is the 18th in a series of 49 occlusions; at this time arterial pH was 7.358, with a lactate of 1.6 mmol l^{-1} . Data are 1 s averages.

the greatest increase in blood pressure observed after umbilical cord occlusion (Figs 1 and 2). Despite this brisk increase in blood pressure, the baroreflex-mediated changes in FHR were still much slower than typical decelerations in labour, which in many cases reach a nadir within 5–10 s (Hon & Quilligan, 1967). In conclusion, although the baroreflex is undoubtedly functional and active during fetal life (Segar *et al.* 1992; Booth *et al.* 2009, 2011), it is mechanically unable to contribute to the typical brief intrapartum deceleration.

Hypovolaemia: the Bezold–Jarisch reflex?

Alternatively, selective compression of the umbilical vein could reduce venous return from the placenta to the fetus sufficiently to reduce central blood volume (Sunderström *et al.* 2000). Potentially, this could trigger the Bezold–Jarisch reflex, whereby reduced blood volume and subsequently reduced cardiac filling pressures activate cardiac C-fibres, and so trigger a vagal deceleration. This reflex allows a longer filling time, restoring stroke volume and so restoring cardiac output (Mark, 1983). However, there is no evidence of reduced atrial (or ventricular) pressures during partial cord occlusion in fetal sheep that would activate this reflex (Itskovitz *et al.* 1987). In contrast, microsphere based measurements during partial occlusion demonstrated an increase in blood flow in the abdominal inferior vena cava and in the proportion of umbilical venous blood passing through the ductus venosus. This illustrates that compensatory preferential shunting maintains venous return to the fetal heart and thus atrial filling pressures are maintained (Itskovitz *et al.* 1987). Although there is evidence that during partial cord occlusion a secondary delayed reduction in FHR occurs in parallel with loss of fetal femoral vascular resistance, which might be consistent with this reflex, this fall in FHR did not occur until after approximately 2 min, well after the initial FHR deceleration (Giussani *et al.* 1997). Finally, the Bezold–Jarisch reflex is also known to be very immature at birth (Gootman *et al.* 1983). Critically, just as with the baroreflex, it is sympathoinhibitory (Mark, 1983) and so wholly inconsistent with the rapid increase in SNS activity during umbilical cord occlusion described above. Thus, it is highly improbable that its activation could contribute to the brief decelerations characteristic of labour.

The peripheral chemoreflex?

The above hypotheses are inviting to both families and clinicians because they suggest that fetuses are not being exposed to asphyxia during decelerations in labour. Aside from head compression, which in systematic studies was only associated with decelerations when it was sufficiently severe as to cause frank cerebral hyperperfusion, it is

important to appreciate that if the hypothesised events described above did occur during labour, they must all be confounded in time with a rapid fall in fetal arterial oxygen saturation (Kunzel *et al.* 1980). As shown in Fig. 1, cerebral oxygenated haemoglobin measured by near-infrared spectroscopy fell within 6 s of complete umbilical cord occlusion in near-term fetal sheep. This fall parallels the simultaneous fall in FHR. This refutes suggestions that hypoxia only occurs once a deceleration is prolonged (Gibbs & Arulkumaran, 2007; Sholapurkar, 2012). In contrast to the questionable mechanisms described above, the peripheral chemoreflex is reliably and rapidly activated during fetal life and so can readily explain the vast majority of intrapartum decelerations.

There is considerable evidence that repeated periods of asphyxia are common during labour, independent of any umbilical cord occlusion (Westgate *et al.* 2007). The fetus is dependent on continuous placental and umbilical blood flow for oxygen delivery. Normal, uncomplicated labours are associated with a small but consistent fall in pH and oxygen tension, and a rise in carbon dioxide tensions, base deficit and plasma lactate, showing that intermittent interruption of placental exchange occurs during all normal labours (Modanlou *et al.* 1974; Huch *et al.* 1977; Wiberg *et al.* 2006). This in turn is consistent with findings that intrauterine pressure increases during contractions and is associated with a linear fall in maternal uterine artery blood velocity of up to 73% during individual contractions (Janbu & Nesheim, 1987). Similar reductions in uterine blood flow have been found in pregnant sheep and dogs (Assali *et al.* 1958). Further, decreased

umbilical artery blood flow was observed during variable decelerations in humans (Sakai *et al.* 1997), and during spontaneous second stage contractions in the bovine fetus (Bleul *et al.* 2007). Clinically, variable, late and prolonged FHR decelerations are universally associated with a rapid reduction in fetal cerebral oxygenation on near-infrared spectroscopy (Aldrich *et al.* 1996). Thus, uterine contractions result in impaired fetal arterial oxygen tensions, regardless of whether or not direct umbilical cord compression occurs.

The peripheral chemoreflex is the response to an acute fall in oxygen tension mediated by the peripheral chemoreceptors. The key efferent arms of the peripheral chemoreflex are the rapid vagal-mediated fall in heart rate, i.e. the deceleration in labour, and SNS mediated peripheral vasoconstriction (Giussani *et al.* 1993). Presumptively, the fall in FHR reduces myocardial work and so helps to conserve cardiac glycogen levels (Bennet *et al.* 2009). Although the peripheral chemoreflex matures during the course of normal gestation (Fletcher *et al.* 2006), it is a robust response throughout pregnancy (Kiserud *et al.* 2001; Wassink *et al.* 2007). The immediate fall in cardiac output due to decreased FHR is offset by SNS-mediated peripheral vasoconstriction. The combined effect of these responses maintains or increases arterial pressure, which in turn maintains or increases blood flow to the 'central organs' such as the brain, heart and adrenals, as recently reviewed (Giussani, 2016). After the initial neural-mediated fall in peripheral blood flow, vasoconstriction is maintained by release of vasoactive mediators (Booth *et al.* 2012; Giussani, 2016), including

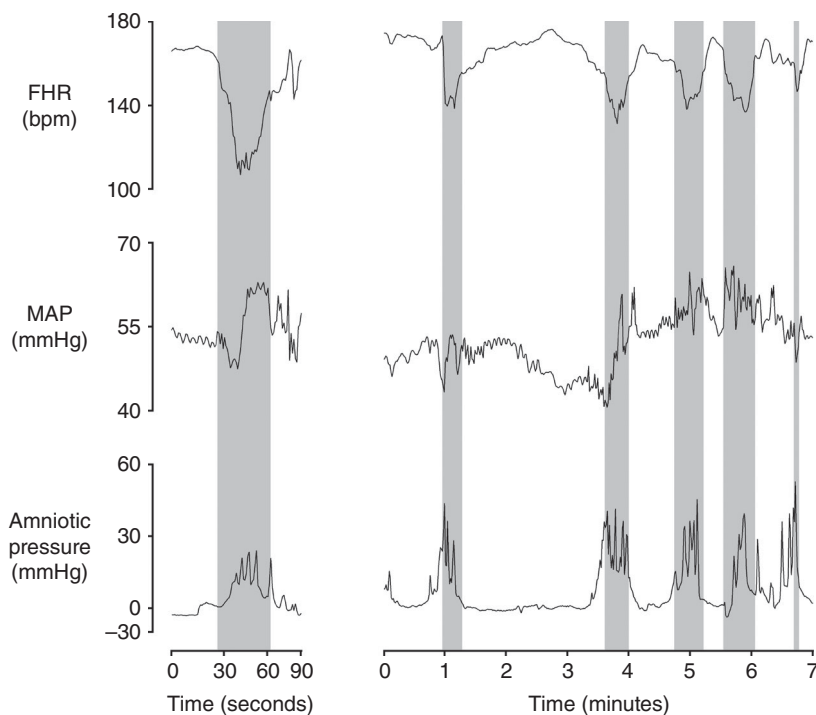


Figure 3. Cardiovascular responses during spontaneous uterine contractions in a near-term fetal sheep (0.85 of gestation)

Fetal heart rate (FHR beats min^{-1} (bpm)), mean arterial pressure (MAP, mmHg) and amniotic pressure (mmHg) during uterine contractions resulting in a deep deceleration (left panels) and multiple moderate decelerations (right panels). Labour was induced by the administration of betamethasone (11.4 mg, i.m. to the ewe x2, 24 h apart) as previously described (Liggins, 1969). Contractions began approximately 48 h after the first dose of betamethasone. Note in the left panels that the deep deceleration occurred despite an initial mild fall in MAP at the start of contraction while delayed hypertension develops late in the deceleration, consistent with the data presented in Figs 1 and 2 during complete umbilical cord occlusion. Only the second to last contraction in the right panels was associated with an increase in MAP at the start of the deceleration. Thus the baroreflex cannot be a consistent trigger of decelerations. Data are 1 s averages.

adrenal catecholamines (Giussani *et al.* 1993; Galinsky *et al.* 2014), vasopressin (Perez *et al.* 1989) and neuropeptide Y (Fletcher *et al.* 2000).

When is the chemoreflex triggered during labour? The vast majority of decelerations occur in association with uterine contractions; the majority of these are unlikely to result in complete cessation of placental and umbilical blood flow. Considering this, fetal oxygenation probably changes dynamically over the course of a contraction, reflecting a balance between the fall in oxygen supply related to contraction strength and duration, and continuing consumption of oxygen by the fetus. The fetus is not a passive player and can decrease oxygen expenditure, increase oxygen extraction and augment shunting of blood to crucial organs to defend itself (Itskovitz *et al.* 1983a; Wilkening & Meschia, 1983; Bocking & Harding, 1986). Experimentally, rapid

decelerations are not triggered until umbilical blood flow is reduced by at least 50% from baseline (Itskovitz *et al.* 1983b; Giussani *et al.* 1997). Thus, the healthy fetus is often able to adapt to mild reductions in oxygen supply without triggering a deceleration and so not all uterine contractions are associated with decelerations. Broadly, as the reduction in utero-placental or umbilical flow becomes greater, the FHR deceleration also becomes deeper (Itskovitz *et al.* 1983b; Baan *et al.* 1993).

In well controlled experimental studies in healthy animals, the magnitude of the peripheral chemoreflex-mediated deceleration is closely correlated with the degree of reduction in utero-placental flow (Peeters *et al.* 1979; Itskovitz *et al.* 1982, 1983a; Baan *et al.* 1993). In labour, many other factors contribute to fetal arterial oxygen saturation over the course of a contraction. As illustrated in Fig. 4, the balance between these factors is crucial in determining the delay before oxygenation is

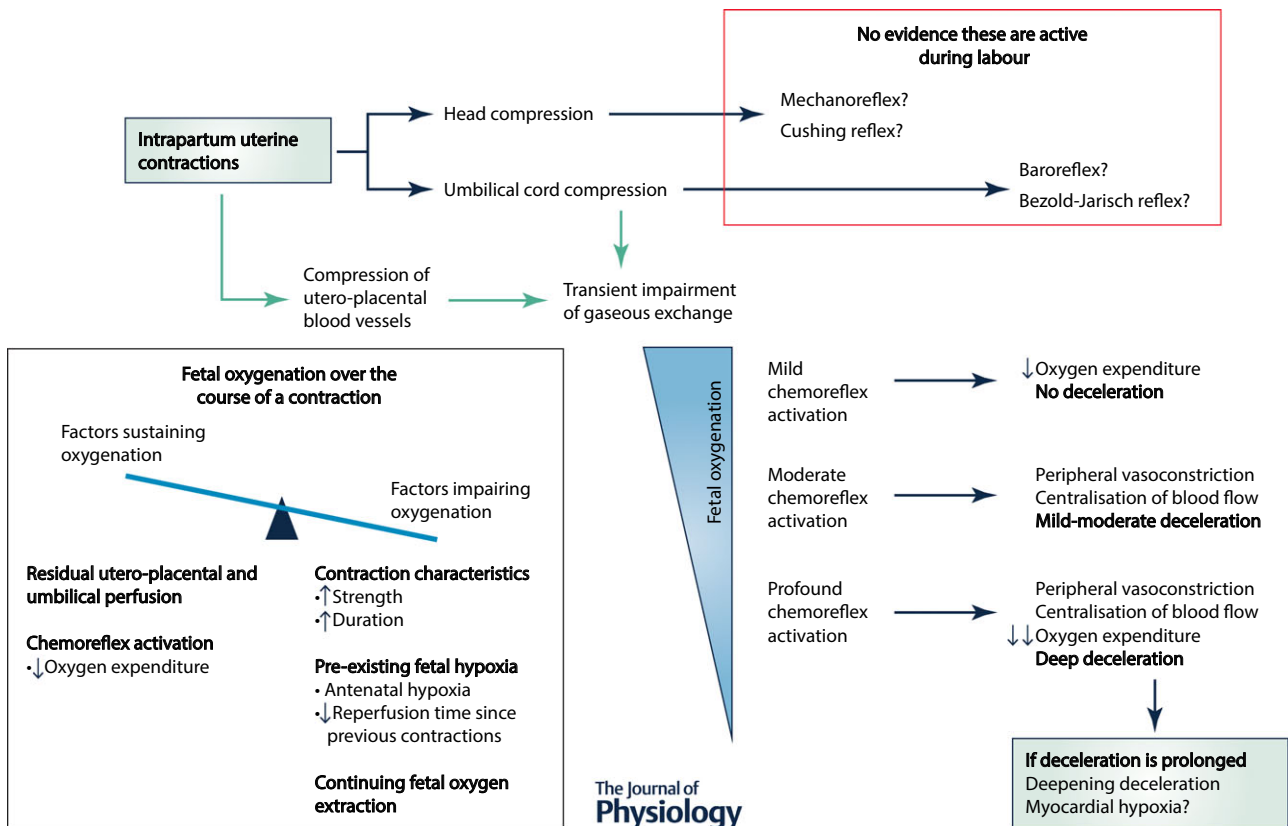


Figure 4. Factors that influence fetal oxygenation over the course of an intrapartum uterine contraction During the course of an individual contraction, there is a critical balance between factors promoting a fall in fetal arterial oxygenation and those that sustain it – the relative strengths of these factors will determine the extent to which fetal arterial oxygenation falls during an individual contraction. Greater strength and duration of a uterine contraction leads to greater impairment of gaseous exchange, while antenatal factors such as impaired utero-placental perfusion can exacerbate the severity of fetal deoxygenation. Fetal oxygen extraction must continue during a uterine contraction; however, the fetus can adapt to this reduced gas exchange by reducing non-vital metabolic and behavioural processes, and so reduce its oxygen consumption. The degree to which fetal oxygenation falls during a contraction will determine the magnitude of the peripheral chemoreflex response, and, in turn, the depth of any resulting deceleration.

impaired sufficiently to trigger a rapid deceleration, as well as the magnitude and duration of the deceleration. An important factor that modulates the magnitude of the fall in fetal oxygen tension is fetal oxygenation status before the contraction. This in turn will be determined by the underlying placental exchange capacity and the duration of placental reperfusion between contractions. Consistent with this, pre-existing hypoxia in fetal sheep has been associated with deeper and longer decelerations, that began earlier, during maternal aortic occlusion (Itskovitz *et al.* 1982).

Does the peripheral chemoreflex evolve over the course of labour? Labour can last for many hours and it is thus important to consider how this prolonged exposure time affects the fetus' ability to respond to repeated interruptions in oxygen supply. During severe asphyxia the neural components of the chemoreflex are relatively short lived, and thus it represents a rapid response system. During a prolonged and severe deceleration (i.e. in response to severe asphyxia) both the vagal and SNS efferent components of the peripheral chemoreflex start to become attenuated after 90–120 s (Barcroft, 1946; Harris *et al.* 1982; Westgate *et al.* 2007; Booth *et al.* 2012).

From this point on, the deceleration is thought to be maintained by the direct effects of 'myocardial hypoxia' (Barcroft, 1946; Westgate *et al.* 2007), while peripheral vasoconstriction is sustained by humoral factors (Galinsky *et al.* 2014). Fortunately, most decelerations (and episodes of asphyxia) during labour are brief, lasting for a minute or less. Indeed, we have shown that both parasympathetic and sympathetic responses rapidly recover between brief repeated complete umbilical occlusions in near-term fetal sheep that were continued for many hours, despite evolving severe metabolic acidosis (Bennet *et al.* 2005; Galinsky *et al.* 2014). Thus, the fetus' crucial autonomic responses to asphyxia can continue to be reactivated by repeated uterine contractions even during prolonged labour.

The next question is whether the responsiveness or magnitude of the peripheral chemoreflex changes over the course of repeated episodes of asphyxia. In fetal sheep, repetition of mild (partial) occlusions that did not result in hypotension or severe acidosis has been associated with attenuation of both the vagal and sympathetic efferents of the peripheral chemoreflex, resulting in a shallower deceleration and less peripheral vasoconstriction with repeated occlusions (Giussani *et al.* 1997; Green *et al.* 1999). In contrast, during repeated complete occlusions of the umbilical cord, leading to worsening hypotension and acidosis, the initial vagal-mediated deceleration became more rapid as fetuses developed progressive cardiovascular compromise with hypotension during occlusions (Bennet *et al.* 2005). Further, there is recent evidence that although the initial sympathetic neural response to support arterial

blood pressure and redistribute cardiac output is transient, it can be repeatedly reactivated between episodes of brief asphyxia over many hours, without becoming attenuated (Galinsky *et al.* 2014; Lear *et al.* 2016).

These data strongly suggest that the peripheral chemoreflex response is not only sustained but the vagal response is augmented by repeated exposure to severe asphyxia. It is likely that the progressive metabolic acidosis itself contributes to augmenting the chemoreflex responses, as shown by the finding that mild acidosis induced by infusion of acidified saline was associated with a greater fall in FHR and increased vasoconstriction of the femoral artery in near-term fetal sheep subjected to moderate hypoxaemia (Thakor & Giussani, 2009).

The contrasting experimental data examined in this section show that the peripheral chemoreflex responses probably do evolve during the course of labour, becoming more rapid (or at least maintained) when fetal survival is threatened, whereas they become relatively attenuated during milder insults that do not lead to significant fetal acidemia. Thus, during mild homeostatic challenges, the fetus probably partially adapts through other mechanisms.

Experimental studies of brief repeated asphyxia – what can be learned about the fetal adaptation to labour?

The above sections illustrate that during labour every fetus is exposed to brief but repeated asphyxia. This statement should not cause alarm. Indeed this is offset by the striking ability of the fetus to adapt to repeated asphyxia, which needs to be appreciated to understand how the clinician should interpret decelerations. Systematic studies in fetal sheep have illustrated that the healthy fetus can adapt almost indefinitely to severe repeated asphyxia without risk of injury, provided that the time between decelerations is sufficient to allow recovery of the oxygen debt. This is strikingly exemplified by the findings that healthy near-term fetal sheep did not develop hypotension despite being exposed to 1 min complete umbilical cord occlusions repeated continuously every 5 min for 4 h. These fetuses showed stable variable decelerations and developed only mild acidosis (nadir of pH 7.34 ± 0.07 , base deficit 1.3 ± 3.9 mmol l⁻¹ and lactate 4.5 ± 1.3 mmol l⁻¹) (Westgate *et al.* 1999a). In contrast, fetuses with pre-existing spontaneous hypoxia developed progressive cardiovascular compromise during repeated umbilical cord occlusions of the same frequency, with severe, progressive metabolic acidosis (nadir of pH 7.07 ± 0.14 , base deficit 14 ± 1.8 mmol l⁻¹ and lactate 10.9 ± 1.9 mmol l⁻¹) and hypotension (nadir of 24 ± 2 mmHg vs. 45.5 ± 3 mmHg in normoxic fetuses; $P < 0.001$) (Westgate *et al.* 2005; Wassink *et al.* 2013).

When the period of time between 1 min umbilical cord occlusions was reduced to 90 s, and so was insufficient

to allow complete recovery between occlusions, even normoxic fetuses ultimately developed profound acidosis (pH 6.92 ± 0.03 , base deficit 19.2 ± 1.5 mmol l⁻¹ and lactate 14.6 ± 0.8 mmol l⁻¹ at the end of the occlusion series) (Westgate *et al.* 2001*b*). These fetuses initially showed a sustained increase in blood pressure during occlusions, but eventually developed a biphasic response to each occlusion, with continuing initial hypertension that was then followed by a rapid fall in blood pressure (de Haan *et al.* 1997; Westgate *et al.* 1999*a*, 2001*a,b*).

Despite these dramatic changes in fetal blood pressure, fetuses continued to show almost identical variable decelerations for many hours of repeated occlusions (de Haan *et al.* 1997). Delayed recovery of the FHR after the end of occlusion was seen only as a near-terminal event, in a minority of fetuses. Despite multiple detailed analyses there is no single consistent FHR marker of fetal compromise (de Haan *et al.* 1997; Westgate *et al.* 1999*a*, 2001*a,b*, 2005, 2007; Bennet *et al.* 2005; Lear *et al.* 2016). Overall, developing fetal acidosis and hypotension appears to be associated with relatively modest changes to the FHR response such as an increase in FHR between decelerations, leading to a greater depth and rate of fall in FHR during each deceleration (Bennet *et al.* 2005). The lack of a strong marker of fetal compromise is consistent with a 4-year retrospective cohort study of 5388 consecutive term singleton labours, which found that the strongest factor associated with acidaemia was the total deceleration area during repetitive decelerations, whereas many features suggested by current clinical guidelines provided no additional predictive power (Cahill *et al.* 2012).

What do intrapartum decelerations tell us about the fetus during labour?

The observation of a brief deceleration tells us that the fetus has experienced a brief period of asphyxia; however, this in itself does not tell us anything about the condition of the fetus. Contrary to one common clinical teaching, whether a pattern of repeated intrapartum decelerations is benign or not does not depend on whether the decelerations are 'reflex'. All brief (<~1–1.5 min) decelerations are reflex in origin. Rather, the risk that hypotension and profound acidosis will develop depends on the balance between the fetus' ability to adapt to repeated hypoxic challenges (largely determined by its placental exchange capacity relative to oxygen consumption) and the time available to recover between occlusions. It is this balance which determines the magnitude of the progressive oxygen debt associated with repeated uterine contractions, as illustrated in Fig. 5.

Decelerations that become deeper and longer over the course of labour reflect more severe and longer periods of interrupted gaseous exchange, respectively. Thus

the severity of the fetal oxygen debt is closely associated with the depth, duration and frequency of intrapartum decelerations (i.e. the cumulative deceleration area). The frequency of decelerations is important as it determines the reperfusion time between asphyxial insults. If there is a sufficient duration of recovery the fetus will overcome its acute oxygen debt and begin to replenish its anaerobic reserves. Crucially, these relationships are all heavily modulated by fetal condition, including the amount of stored cardiac glycogen (Dawes *et al.* 1959) and the adequacy of the pre-labour placental exchange capacity (Westgate *et al.* 2005; Wassink *et al.* 2013).

Supporting these preclinical findings, clinically it is well established that conditions associated with antenatal hypoxia and growth restriction are also associated with increased risk of neonatal encephalopathy and an overall increase in perinatal morbidity and mortality (Nicolaidis *et al.* 1989; Westgate *et al.* 1999*b*; Nelson *et al.* 2012; McIntyre *et al.* 2013). Unfortunately, the overall appearance of decelerations does not appear to alter substantially despite the progressive development of fetal compromise – a testament to how robust the peripheral chemoreflex truly is.

What is left unanswered?

Why are late decelerations associated with fetal compromise? Little is known about the pathophysiology behind late decelerations and why they have been (inconsistently) seen in compromised fetuses (Thomas, 1975; Fleischer *et al.* 1982; Sameshima & Ikenoue, 2005; Parer & Ikeda, 2007; Cahill *et al.* 2012). Late decelerations are defined by a lag between the contraction and the beginning of the deceleration. As previously reviewed (Westgate *et al.* 2007), it is important to distinguish between two types of 'late' decelerations.

Firstly, the true late decelerations consistent with Hon's original description occur before labour, and are often accompanied by baseline tachycardia, low to absent variability and absent accelerations. These are usually observed with painless uterine 'tightenings' or contractures. The predominant clinical scenario is a mother who reports reduced fetal movements, or a known growth restricted fetus with reduced fetal movements. This setting suggests that the fetus probably has poor utero-placental perfusion and is thus unable to adapt to even the small decreases in placental exchange associated with mild contractures without triggering a deceleration. If the fetus is still neurologically intact, this deceleration will still represent a peripheral chemoreflex response. This antenatal pattern appears to identify the compromised fetus who will not adapt to the stress of labour, as previously reviewed (Westgate *et al.* 2007).

In contrast, intrapartum 'late' decelerations are almost always simply variable decelerations that are late in timing.

There is no evidence that these late decelerations are associated with a greater physiological challenge to the fetus than early or variable decelerations (Westgate *et al.* 2007; Cahill *et al.* 2012). It is unknown why there is a lag time between contraction and deceleration. Presumptively, the delay is related to the time taken for fetal oxygenation to become impaired sufficiently to trigger a deceleration and then to recover.

What is 'myocardial hypoxia'? It is well known that complete parasympathetic blockade only delays the onset of a FHR deceleration by approximately 90–120 s during sustained, severe asphyxia (Barcroft, 1946; Westgate *et al.* 2007). This is believed to represent the direct depressant effects of hypoxia on the heart. However, more

research is needed to understand the specific mechanisms. For example, accumulation of the cardiodepressant adenosine is reported to contribute in part to bradycardia during prolonged moderate hypoxia (Giussani *et al.* 2001), but its role during more severe insults is unclear.

As discussed previously, in intact fetuses it is believed that the peripheral chemoreflex is replaced by myocardial hypoxia during deep decelerations if they are prolonged, although there is no specific evidence from measurements of fetal vagal activity to directly confirm inhibition of parasympathetic activity. Nonetheless, the point at which myocardial hypoxia contributes to a deceleration probably reflects the transition from a period of asphyxia that was completely compensated for by the fetus, and one that

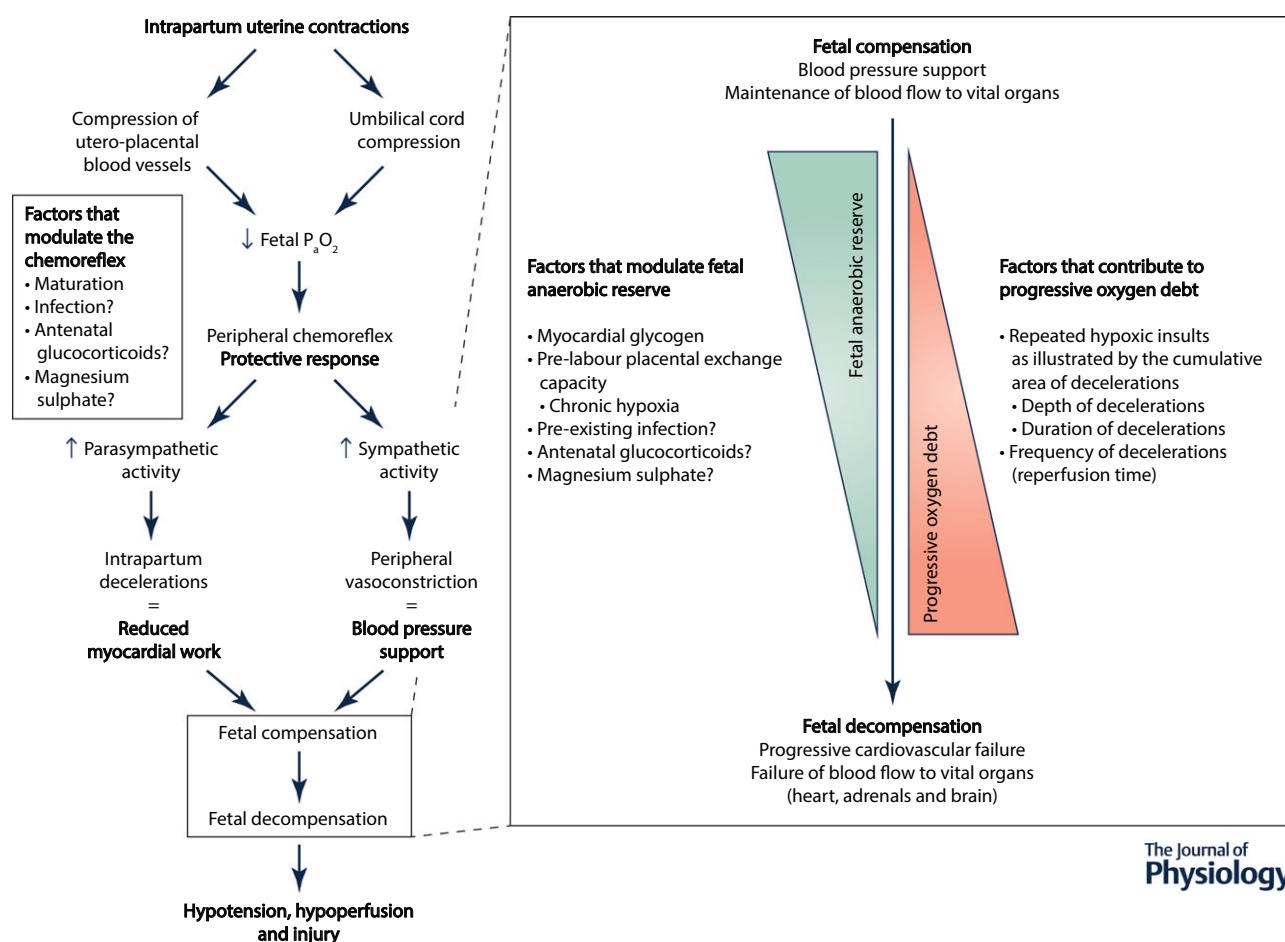


Figure 5. Factors that influence fetal anaerobic reserve and fetal oxygen debt during labour

Periods of brief asphyxia are frequent and a normal component of labour. This is offset by the fetus' ability to adapt to these challenges through peripheral chemoreflex activation and a high anaerobic tolerance. Thus, the vast majority of fetuses adapt effectively to labour and are born healthy. The ability to adapt is finite, however, and can fail in two situations. Firstly, a fetus with good antepartum health and adequate anaerobic reserves can progressively decompensate if exposed to severe repeated asphyxial challenges that are too frequent to allow complete recovery between intense uterine contractions. Secondly, and perhaps of more clinical importance, is the scenario of a fetus entering labour with poor utero-placental exchange capacity and reduced glycogen reserves. Such fetuses are unable to fully compensate to the repeated asphyxial challenges of a typical labour and will quickly decompensate, leading to hypotension and increasing risk of neural injury.

was not. Thus a marker of such a transition is likely to be clinically useful.

We believe this transition is, albeit imperfectly, reflected by the development of overshoot tachycardia immediately after a deceleration. Overshoot tachycardia refers to a large increase in FHR immediately after a deceleration that can last up to 10–30 s. It should be distinguished from the so-called ‘shoulders’ that can occasionally be observed clinically. Overshoot can be seen in association with either a normal or increased baseline FHR (Westgate *et al.* 2007). In fetal sheep, overshoot tachycardia was observed in association with the development of acidosis and hypotension after brief 1 min umbilical cord occlusions repeated every 2.5 min (Westgate *et al.* 2001*b*). In contrast, overshoot tachycardia was observed immediately from the first occlusion onwards during longer, 2 min, repeated occlusions when fetuses were neither acidotic nor hypotensive (Westgate *et al.* 2001*b*, 2007; Lear *et al.* 2016). Thus overshoot is not a consistent marker of fetal compromise. Nevertheless, it does appear to indicate the loss of vagal tone, and likely accompanying myocardial hypoxia, during an individual deep deceleration.

Where do the afferent chemoreflex signals originate? In strong contrast to the response to moderate acute hypoxia, where carotid chemodenervation completely prevents any fall in FHR (Itskovitz & Rudolph, 1982; Bartelds *et al.* 1993; Giussani *et al.* 1993), isolated carotid chemodenervation only slows the fall in heart rate during severe asphyxia (Jensen & Hanson, 1995). These data suggest that there are substantial unidentified afferent inputs that can stimulate the peripheral chemoreflex. Speculatively, one key additional input might be greater recruitment of aortic chemoreceptors during severe asphyxia (Hanson, 1997).

The role of central chemoreceptors in fetal life is also poorly described but they are probably more sensitive to changes in the partial pressure of carbon dioxide and pH than to oxygen levels, as is the case in adults (Nattie, 2006). In light of this, they probably provide longer-term feedback on the acid–base status of the fetus and, speculatively, may contribute to the modulation of peripheral chemoreflex responses during repeated insults as discussed above.

How do maturation and additional factors affect peripheral chemoreflex responses? Although the peripheral chemoreflex is known to be active from very early in gestation, and the preterm fetus is known to have a qualitatively similar response to severe prolonged asphyxia to that seen at term (Gunn *et al.* 2001; Wassink *et al.* 2007), there is limited evidence on how preterm fetuses adapt to the repeated asphyxial insults characteristic of labour (Keunen & Hasaart, 1999), or whether fetal responses are

modulated by exposure to chronic intrauterine infection or inflammation (Booth *et al.* 2013). For example, the cortisol surge that occurs later in gestation is associated with further maturation of the peripheral chemoreflex response to moderate hypoxaemia (Fletcher *et al.* 2006). It is unclear how this alters the peripheral chemoreflex response to the more severe homeostatic challenge of repeated asphyxia. The effects of many common clinical drugs are also not fully understood. In the fetal sheep, exposure to maternal dexamethasone is associated with a more prolonged deceleration during acute moderate hypoxia (Fletcher *et al.* 2003; Jellyman *et al.* 2005). Further, maternal treatment with magnesium sulphate can reduce baseline FHR, in addition to its known vasodilatory effects (Nensi *et al.* 2014; Galinsky *et al.* 2016). Thus, it is clearly important to determine how these treatments affect the ability of the fetus to sustain peripheral chemoreflex responses to repeated severe asphyxia in labour.

The way forward: physiology over descriptive titles

There is now overwhelming evidence that brief FHR decelerations in labour are mediated by the peripheral chemoreflex, and are related to acute but brief asphyxia. The complex and un-physiological explanations described at the start of this review probably arose to try to explain why many babies are born without acidosis despite repeated decelerations during labour. The experiments reviewed above show that this apparent discrepancy is the result of the truly remarkable ability of the healthy mammalian fetus to adapt to the short periods of asphyxia characteristic of labour without systemic compromise (Westgate *et al.* 2001*a*, 2005).

Consistent with decelerations being predominantly mediated by peripheral chemoreflex activation, there is considerable evidence that the clinical practice of classifying decelerations based on shape and timing does not improve the obstetrician’s ability to identify acidotic fetuses (Parer & Ikeda, 2007; Cahill *et al.* 2012). Similarly, the recent large retrospective study from Cahill and colleagues found that the cumulative area of decelerations is one of the best available measures of progressive fetal oxygen debt during labour (Cahill *et al.* 2012). Thus, we believe that when it comes to interpreting decelerations it is better to focus on the frequency, depth and total duration of decelerations during labour rather than on the timing, shape or supposed aetiology of specific decelerations. This of course must take into account the overall clinical context of these decelerations, and would include evaluation of baseline FHR, FHR variability, contraction frequency and, importantly, the evolution of all of these features over the course of labour, coupled with knowledge of relevant clinical factors.

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Additional information

Competing interests

None declared.

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