Deceleration area and capacity during labour-like umbilical cord occlusions identify evolving hypotension: a controlled study in fetal sheep

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Short title

Deceleration area, capacity and hypotension.

Abstract

Objective: Cardiotocography is widely used to assess fetal well-being during labour. The positive predictive value of current clinical algorithms to identify hypoxia-ischaemia is poor. In experimental studies, fetal hypotension is the strongest predictor of hypoxic-ischaemic injury. Cohort studies suggest that deceleration area and deceleration capacity of the fetal heart rate trace correlate with fetal acidaemia, but it is not known if they are indices of fetal arterial hypotension.

Design: Prospective, controlled study.

Setting: Laboratory.

Sample: Near-term fetal sheep.

Methods: 1 min of complete umbilical cord occlusions (UCOs) every 5 min (1:5min, n=6) or every 2.5 min (1:2.5min, n=12) for 4 h or until fetal mean arterial blood pressure fell <20mmHg.

Main Outcome Measures: Deceleration area and capacity during the UCO series were related to evolving hypotension.

Results: The 1:5min group developed only mild metabolic acidaemia, without hypotension. By contrast, 10/12 fetuses in the 1:2.5min group progressively developed severe metabolic acidaemia and hypotension, reaching 16.8±0.9mmHg after 71.2±6.7 UCOs. Deceleration area and capacity remained unchanged throughout the UCO series in the 1:5 min group, but progressively increased in the 1:2.5 min group. The severity of hypotension was closely correlated with both deceleration area ($p<0.001$, $R^2=0.66$, n=18) and capacity ($p<0.001$, $R^2=0.67$, n=18). Deceleration area and capacity predicted development of hypotension at a median of 103 and 123min before the final occlusion, respectively.

Conclusions: Both deceleration area and capacity were strongly associated with developing fetal hypotension, supporting their potential to improve identification of fetuses at risk of hypotension leading to hypoxic-ischaemic injury during labour.

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Keywords: Hypoxia-ischaemia, asphyxia, cardiotocography, computerised fetal heart rate monitoring, deceleration area, deceleration capacity, phase rectified signal averaging, hypotension

Tweetable abstract: Deceleration area and capacity of fetal heart rate identify developing hypotension during labour-like hypoxia

Introduction

Cardiotocography (CTG) monitoring of fetal heart rate (FHR) and uterine contractions is widely used to assess fetal well-being during labour. A normal FHR recording identifies fetuses who are tolerating the stress of labour but abnormal FHR patterns have a low positive predictive value for fetal acidaemia or hypoxic-ischaemic injury.[1-4] The total deceleration area (DA), integrating the depth, duration and frequency of FHR decelerations, is a potential measure of fetal hypoxic stress in labour.[5-7] It is difficult to quantify visually and early computerisation attempts were hampered by technological constraints. Encouragingly, recent, large cohort studies of labour at term found that DA is more strongly associated with fetal acidaemia and/or neonatal condition than standard clinical assessment.[8-14] For example, retrospective cohort studies, involving 5,388 and 1,630 labours, respectively, reported that DA was the strongest index of neonatal acidaemia.[8, 13] This association was supported by a prospective study of the last 120 min of labour in 8,580 women.[9]

Another potential index of the burden of decelerations is deceleration capacity (DC). It has been used as a measure of heart rate variability,[15-17] but can be adapted to average the magnitude of all falls in FHR between successive heartbeats and so provide an integrated measure of the magnitude and frequency of FHR decelerations,[12, 15] DC has been shown to predict acidaemia or fetal compromise in a cohort study of >22,000 human labours[10] and to be associated with acidaemia in fetal sheep.[18] DC does not rely on correctly identifying baseline FHR and decelerations, as is required to measure DA, and it is very tolerant of noise and loss of contact during FHR recording. Thus, DC may be useful for computerised FHR analysis, providing a surrogate for DA that avoids some of its practical constraints.

One limitation of the clinical studies is that their primary outcome was acidosis at birth. Fetal acidosis is highly affected by the pattern of hypoxia and by fetal metabolism of lactate, and so is weakly associated with risk of brain injury in clinical [19] and preclinical studies.[20] The

development of hypotension during severe or recurrent hypoxia critically compromises cerebral perfusion and so precipitates hypoxic-ischaemic injury across multiple animal models.[21-23] Unfortunately, it cannot be measured in human labour. In the current study we tested the hypothesis that DA and DC would be associated with the development of hypotension in near-term fetal sheep exposed to a series of complete brief umbilical cord occlusions (UCOs),[24-28] repeated at a frequency consistent with that of contractions in labour.[29]

Methods

Surgical preparation

Eighteen Romney/Suffolk fetal sheep were surgically instrumented at 116-122 days gestation under sterile conditions.[30] Ewes received oxytetracycline (20mg/kg, Phoenix Pharm Distributors, Auckland, NZ) intramuscularly 30 min before surgery. Anaesthesia was induced with intravenous propofol (5 mg/kg, AstraZeneca, Auckland, NZ), followed by 2-3% isoflurane in oxygen. During surgery, ewes received an intravenous infusion of 200 ml/h of isotonic saline. The uterus was exposed through a midline abdominal incision, and the fetus was partially exposed. Polyvinyl catheters (SteriHealth, Dandenong South, VIC, Australia) were placed in the femoral artery to measure MAP, the brachial artery for pre-ductal blood sampling and the amniotic sac to correct for maternal position. Electrodes (AS633-5SSF, Cooner Wire, Chatsworth, CA, USA) were placed across the fetal chest to measure the electrocardiogram (ECG). An inflatable silicone occluder was placed around the umbilical cord to allow UCOs (18HD, In Vivo Metric, Healdsburg, CA, USA). In the case of twin pregnancies, only one fetus was surgically instrumented.

Gentamicin was injected into the amniotic sac (80 mg, Pfizer, Auckland, NZ) and the uterus was closed. Long-acting local analgesic (0.5% bupivacaine plus adrenaline, AstraZeneca) was infiltrated into the maternal midline skin incision. Fetal leads were exteriorised through the maternal flank. A maternal long saphenous vein was catheterised for post-operative care.

Post-operative care

Ewes were housed together in temperature-controlled rooms (16±1°C, humidity 50±10%) with a 12 h light/dark cycle with lights on at 0600 h, in separate metabolic cages, with *ad libitum* access to food and water. Daily intravenous antibiotics were administered to the ewe for 4 days (600mg benzylpenicillin sodium; Novartis, Auckland, New Zealand, and 80mg gentamicin).

Patency of the fetal catheters was maintained by continuous infusion of heparinised saline (20U/ml at 0.2ml/h).

Recordings

All signals were digitised at 4096 Hz, decimated to lower sampling rates and stored using LabVIEW-based software (National Instruments, Austin, TX, USA). MAP was recorded using Novatrans III Gold, MX860 pressure transducers (Medex, Hilliard, OH, USA) and corrected for maternal position by subtraction of amniotic fluid pressure. The pressure signals were amplified 500×, low-pass filtered with a Butterworth-filter at 20Hz and saved at 64Hz. The raw electrocardiogram signal was analogue filtered with a first-order high-pass filter at 1Hz and an eighth-order low-pass Bessel-filter set at 100Hz and saved at 512Hz.

Experimental protocol

UCOs were performed at 120-126 days gestation (term gestation is 147 days). At this time neural development of the fetal sheep is broadly similar to that of term human infants.[31] Fetuses were randomly assigned to receive complete UCO for 1min repeated after either 4min reperfusion (i.e. an occlusion every 5min: 1:5-group, n=6) or 1.5min reperfusion (i.e. an occlusion every 2.5 min: 1:2.5-group, n=12). The experimental protocols began at 9 am. For each UCO the occluder was inflated with a volume of saline known to completely occlude the umbilical cord and then released after 1 min, allowing restoration of umbilical blood flow. This was continued for up to 4 h or until MAP fell to <20mmHg during two successive UCOs or failed to recover to baseline values when the next UCO was due. The 1:5 and 1:2.5 occlusion protocols are consistent with the frequency of uterine contractions during the early first stage and the late first stage/second stage of labour, respectively.[29]

Fetal arterial blood samples (0.3 mL) were taken before the start of UCOs, after every 6th and the final UCO. Arterial samples could not be obtained from one fetus in the 1:2.5-group (n=11). Samples were analysed for pH, blood gases (ABL 800, Radiometer, Copenhagen, Denmark),

glucose and lactate (YSI 2300, Yellow Springs, OH, USA). 72 h after the final UCO sheep were killed by intravenous overdose of pentobarbital sodium to the ewe (9g Pentobarb300, Chemstock International, Christchurch, NZ).

Data extraction and time-points

The primary analysis of physiological data was undertaken using LabVIEW-based software. Continuous 1s means of FHR and MAP were derived from the ECG and arterial pressure waveform, respectively. Baseline was defined as the 60 min before UCOs began. In order to account for the unequal duration of individual experiments in the 1:2.5-group, due to fetuses reaching the endpoints defined above at different times, the data in both groups were analysed in four epochs: the first 20 min of UCOs, the middle 20 min of UCOs, the penultimate 20 min of UCOs and the final 20 min of UCOs. For the 1:2.5-group these four epochs represent the initial fetal adaptation associated with sustained hypertension (first 20 min), maintenance of arterial pressure (middle 20 min), the progressive onset of hypotension (penultimate 20 min) and severe hypotension (final 20 min).[32]

During each epoch, computerised FHR indices were calculated from R-R interval data (as described below). The R-R intervals were calculated using a wavelet based algorithm in LabVIEW. The ECG signal was preprocessed using a wavelet transformation, the Daubechies6 (db06) wavelet, to remove both low frequency trends and high frequency noise from the signal. The R peaks were detected on the detrended, denoised ECG signal using multiresolution wavelet analysis. Any peaks above a threshold calculated every 5s as half the maximum height of the ECG signal during that 5s were counted as R peaks.

The minimum MAP was determined as the third-centile, to avoid selection of artifactually low pressures. The minimum MAP could be identified from any time within each epoch, but in practice it corresponded with the MAP recorded at the end of or shortly after UCOs. Fetal

biochemistry was assessed at the same epochs as the physiological data. Biochemistry during the final epoch reflects the arterial sample taken immediately after the final UCO.

Deceleration area and capacity

FHR metrics were calculated using automated algorithms by the Oxford system for intrapartum FHR analysis, as previously published.[15, 33, 34] The algorithms to detect baseline and decelerations are based on signal processing methods for filtering and heuristic thresholds, optimised to fit expert evaluation of intrapartum CTGs from both healthy and severely compromised infants.[35, 36] DA and DC were calculated as the average of two overlapping 15min epochs, moved with a 5min step. DC was calculated as previously described in human intrapartum FHR traces.[10, 15] DC was derived from the phase-rectified signal averaging algorithm (PRSA; T=1, L=11),[17] which interrogates repeating fluctuations between successive heartbeats. Simplistically, every 1s average of FHR that decreased relative to the previous 1s average (i.e. FHR slowed between successive data-points) was defined as a "deceleration anchor". A window of 2L (i.e. 22s) is defined around every anchor, consisting of the anchor itself '$x(0)$', the 11 data-points immediately following the anchor '$x(1)$, $x(2)$, … $x(11)$' and the 10 data-points immediately preceding the anchor '$x(-10)$, $x(-9)$, … $x(-1)$, $x(0)$'. All windows within the analysis epoch are then aligned at the anchor (windows are thereby 'phase-rectified'). Each set of data-points within the aligned windows are then averaged to calculate $\bar{x}(-10)$, $\bar{x}(-10)$, …$\bar{x}(11)$. DC is finally calculated as:

$$\mathrm{DC} = \frac{[\bar{x}(-10) + \bar{x}(-9) + \cdots \bar{x}(0)] - [\bar{x}(1) + \bar{x}(2) + \cdots \bar{x}(11)]}{22}$$

DA was calculated to estimate visual assessment of DA[9] as the sum of deceleration areas in the respective epoch, with each area calculated as:

$$\mathrm{DA} = \frac{\mathrm{Duration} \times \mathrm{depth}}{2}$$

Deceleration amplitude relative to the immediate baseline FHR was calculated. Both minimum MAP and the mean deceleration amplitude were calculated from the average of the same two overlapping 15min epochs as used for DA and DC calculation.

Statistics

Data were analysed using SPSSv25 (IBM, Armonk, NY, USA). Analysis of time series data including MAP and FHR variables was performed by two-way ANOVA, with the four epochs during UCOs treated as repeated measures. If a significant effect of group or an interaction between group and time was identified, individual epochs were compared by one-way ANOVA. Biochemical data were compared between groups by ANOVA, with time treated as a repeated measure. Baseline was used as a covariate if a significant difference was observed in baseline values. The Bland and Altman method was used to investigate the within-subjects relationship between MAP and FHR metrics as well as between MAP and deceleration amplitude using the data from the four epochs.[37] The within-subjects relationships between deceleration amplitude, DA and DC were also calculated. We additionally assessed the performance of DA and DC by investigating the point at which they predicted fetuses destined to develop severe hypotension (i.e. those who reached the MAP target of <20 mmHg). For this analysis, we assessed the entire FHR recordings rather than the discrete epochs presented in figures. Data are means±SEM unless otherwise stated. Statistical significance was accepted when $p<0.05$.

Results

Group characteristics

The 1:5-group was comprised of 4 females, 2 males, 3 singletons and 3 twins, with a post-mortem body weight of 3.93±0.15 kg. The 1:2.5-group was comprised of 3 females, 7 males, 2 unrecorded sex, 6 singletons, 5 twins, 1 unrecorded parity, with a post-mortem body weight of 3.90±0.19 kg.

Biochemistry and blood pressure

Mild metabolic acidaemia (final pH 7.35±0.03, base excess -0.5±1.3 mmol/L, lactate 4.7±1.6 mmol/L) developed in the 1:5-group compared to severe metabolic acidaemia in the 1:2.5-group (final pH 6.95±0.04, base excess -17.7±1.8 mmol/L, lactate 13.7±1.0 mmol/L, all $p<0.05$ vs. 1:5-group). Full arterial blood gas results are reported in Table S1. All fetuses in the 1:5-group maintained normal or increased blood pressure throughout the UCO series, without hypotension (Figure 1A) and all fetuses received the full 49 UCOs over 4 h. By contrast, the 1:2.5-group progressively developed hypotension ($p<0.01$), showing a significant reduction in minimum MAP during the penultimate and final epochs compared to the 1:5-group (both $p<0.001$, Figure 1A). Within the 1:2.5-group, 10/12 fetuses reached MAP <20mmHg on two successive UCOs (final MAP 16.8±0.9 mmHg) by 71.2±6.7 UCOs (3.0±0.3 h). Note that final minimum MAP reported in Figures and Table 1 are higher due to the use of 3rd-centile values for the present analysis. 2/12 fetuses did not reach the MAP target and therefore were exposed to 4 h of UCOs (whole group average 3.1±0.3 h), ending with minimum MAPs at the final UCO of 43.5 and 31.3 mmHg, respectively (whole group average 19.9±2.4 mmHg). These two fetuses (2 males, 1 singleton, 1 twin) were found to have relatively higher post-mortem weights (4.59±0.20 kg) than the 1:2.5-group average; there were no other apparent differences in initial blood gas or physiological values.

Deceleration area, capacity and amplitude

During the UCO series there was a significant effect of group on both DA ($p<0.001$, two-way ANOVA) and DC ($p<0.001$, two-way ANOVA, Figure 1A). Overall, DA and DC increased in first 20 min epoch in both groups. Subsequently, values remained stable in the 1:5-group. By contrast, DA and DC continued to progressively increase in 1:2.5-group such that DA in the 1:2.5-group was greater than the 1:5-group during the middle ($p<0.01$, one-way ANOVA), penultimate ($p<0.001$, one-way ANOVA) and final epochs ($p<0.001$, one-way ANOVA). Similarly, DC in the 1:2.5-group was greater than the 1:5-group during the first ($p<0.05$, one-way ANOVA), middle ($p<0.05$, one-way ANOVA), penultimate ($p<0.005$, one-way ANOVA) and final epochs ($p<0.001$, one-way ANOVA). The relationship between MAP and DA/DC during the UCO series in individual fetuses is shown in Figure 2.

Deceleration amplitude showed an interaction between group and time ($p<0.05$, two-way ANOVA), such that it was increased in the 1:2.5-group during the final epoch compared to the 1:5-group ($p<0.05$, one-way ANOVA, Figure 3A). There was a trend to increased deceleration amplitude in the 1:2.5-group during the penultimate epoch ($p=0.051$, one-way ANOVA).

Performance of deceleration area and capacity

We undertook additional analysis to identify thresholds for DA and DC that would predict fetuses that developed hypotension (<20 mmHg). This analysis was not confined to the four epochs displayed in Figures 1-3. All fetuses that developed severe hypotension crossed thresholds of 6500 bpm^2 for DA and 9 bpm for DC during the UCO series. These thresholds achieved 100% sensitivity and 100% specificity and identified at risk fetuses at a median of 103 min (DA) or 123 min (DC) before the final occlusion, at a time when fetuses had not developed hypotension (median at that time for DA 46 mmHg, DC 43 mmHg). The times that these thresholds were first reached in individual fetuses are shown in Table 1. These are high thresholds that could be crossed several times over time in individual fetuses. As shown in

Figure 2, 8/10 (DA) and 7/10 (DC) fetuses developing hypotension were still above these thresholds during the final epoch. All remaining fetuses remained above the values of those of the 1:5-group.

Relationships between FHR metrics and arterial pressure

The within subjects relationships between hypotension and both DA and DC were investigated by correlating the minimum MAP with simultaneous DA and DC values using data pooled from all four epochs across both the 1:5 and 1:2.5-groups (therefore n=18, each contributing four data-points). Minimum MAP was inversely correlated with both DA ($p<0.001$, $R^2=0.66$, n=18) and DC ($p<0.001$, $R^2=0.67$, n=18, Figure 1B).

Similarly, there was a significant within-subjects correlation between minimum MAP and deceleration amplitude ($p<0.001$, $R^2=0.59$, n=18, Figure 3B). Finally, there were significant within-subject correlations between DA and DC ($p<0.001$, $R^2=0.75$, n=18, Figure 1C) and of deceleration amplitude with both DA ($p<0.001$, $R^2=0.92$, n=18, Figure 3C) and DC ($p<0.001$, $R^2=0.77$, n=18, Figure 3C).

Relationships between acidaemia, FHR metrics and arterial pressure

There were strong, positive within-subject correlations between acidosis and minimum MAP ($p<0.001$, $R^2=0.81$, n=17, Figure S1A). Significant within-subject correlations were identified between acidosis and both DA ($p<0.001$, $R^2=0.645$, n=17, Figure S1B) and DC ($p<0.001$, $R^2=0.639$, n=17, Figure S1B).

Discussion

Main findings

This study demonstrates that in fetal sheep exposed to brief UCOs repeated at rates consistent with the frequency of uterine contractions in either early labour or late first stage/second stage labour,[29] a progressive increase in DA or DC was associated with progressive fetal hypotension. To the best of our knowledge, this is the first time that FHR metrics have been shown to predict fetal hypotension, which is central to the pathogenesis of hypoxic-ischaemic encephalopathy.[21-23] These findings support the use of computerised DA and DC to improve identification of fetuses at risk of intrapartum hypoxia-ischaemia.

Strengths and limitations

The major strength of this study is that we assessed the simultaneous relationship between DA and DC and evolving arterial hypotension. This is not clinically possible, necessitating the use of surrogate measures such as pH, or rare outcomes such as neonatal encephalopathy. The frequencies of UCOs used in this study are highly relevant to that of uterine contractions during human labour. Contractions during the early first stage occur at a comparatively low frequency of approximately 2 per 10 min (1 per 5 min)[29] and increase during the late first stage onwards to 4-5 per 10 min (~1 per 2.5 min).[29, 38] The median duration of the late first and second stage in nulliparous women is between 3.8-4.3 h and 0.2-1.1 h, respectively.[39] It is therefore not uncommon for fetuses to be exposed to 3-4 h of contractions at 4-5 per 10 min, consistent with the average duration of our 1:2.5 UCO group (3.1±0.3 h). By contrast to studies that used pH as the endpoint and did not induce significant neural injury,[40, 41] we targeted a level of hypotension (final MAP 16.8±0.9 mmHg) that is sufficiently severe to cause cytotoxic cerebral oedema, cortical and subcortical neuronal death, focal cerebral infarctions,[24] and

subendocardial injury.[27] The present findings are therefore highly relevant to intrapartum hypoxia-ischaemia.

This study was a controlled experiment using a highly structured protocol of complete UCOs, which cannot fully capture the heterogeneity and dynamics of intrapartum uterine contractions. There are obvious scenarios in which DA and DC will likely show lower utility, such as isolated sentinel events, or fetal growth restriction, which can present with repeated shallow decelerations in early labour.[42] The key limitation of DA and DC is that they do not provide direct information on how well an individual fetus is adapting.[32, 43] Effectively, DA and DC assess risk based on threshold values that a healthy fetus should be able to tolerate. This highlights the need for DA and DC thresholds to be adjusted in future studies, based on antenatal and intrapartum risk factors, as previously reported for DC in large human cohorts.[10]

Interpretations

Similarly to previous studies,[28, 44, 45] the 1:5-group showed sustained cardiovascular adaptation throughout 4 h of UCOs, with stable values of DA and DC over time, mild acidaemia and without hypotension. By contrast, 10/12 fetuses exposed to the 1:2.5 protocol initially adapted well to UCOs but then progressively developed worsening hypotension. Evolving hypotension was accompanied by a progressive rise in both DA and DC.

In part, the difference in DA and DC between the groups is predictable as the 1:2.5-group were exposed to twice the frequency of UCOs and therefore had twice the number of decelerations in any analysed epoch, such that DC but not DA was higher in the 1:2.5-group during the first epoch. However, both DA and DC progressively increased in the 1:2.5-group even though the frequency and duration of UCOs remained constant. Within-subjects analysis confirmed that both DA and DC increased in association with developing fetal hypotension. Conversely, two fetuses exposed to the 1:2.5 protocol did not develop hypotension and showed low DA and DC

values, similar to those of the 1:5-group. Further, the amplitude of decelerations increased during the final epoch in the 1:2.5-group and also correlated with worsening hypotension. This illustrates that deepening decelerations are a sign of fetal compromise, consistent with our previous report.[45] This effect was likely augmented by a progressive increase in the rate at which FHR falls during UCOs repeated at a rate leading to fetal compromise.[45] Finally, a secondary fall in FHR within the first minute after recovery from decelerations was observed in some fetuses, which contributed to the final DA and DC values. This pattern has been previously noted in a subset of fetuses during severe fetal compromise.[28]

Although historically it has been suggested that only 'late' decelerations reflect fetal hypoxaemia, it is now clear that this is not correct. The vast majority of intrapartum decelerations, regardless of their shape and timing, are mediated by activation of the peripheral chemoreflex during acute fetal hypoxaemia.[32, 43, 46] The utility of DA and DC in clinical studies, and experimentally in the present study, suggests that these metrics represent broad indices of the cumulative exposure to recurrent severe hypoxaemia.[43, 47]

We identified threshold values for DA (6500 bpm^2) and DC (9 bpm) that achieved 100% sensitivity and 100% specificity in predicting fetuses that developed hypotension, at a median of 103 (DA) and 123 (DC) minutes before the final UCO. Critically, this was well before fetuses developed hypotension (Table 1 and Figure 2). These DA and DC values represent high thresholds that fetuses could cross several times during the occlusion series. 2/10 (DA) and 3/10 (DC) fetuses that developed severe hypotension had values below these thresholds during the final epoch (Figure 2), albeit their DA and DC values remained higher than the 1:5-group. Our findings suggest that although DA and DC increase progressively with evolving hypotension, this may be interspersed by periodic spikes that may have additional utility as an early warning of hypoxic stress severe enough to lead to hypotension. These findings must be interpreted cautiously considering the highly structured protocols used in our study and the

high variation in the time to final UCO. The reader should note that these thresholds are higher than thresholds suggested by human cohorts.[9, 10]

The progressive worsening of hypotension and increase in both DA and DC throughout the experiment were also associated with decreasing pH (Figure S1). Although these findings suggest DA and DC are associated with worsening fetal acidaemia, it is important to reflect that the relationship between pH and fetal compromise is considerably more complex clinically than in a single, highly structured experiment such as the present study.[19, 20] Finally, although DA corresponds better to clinical guidelines, the present findings suggest that DC is equivalent to DA, but may be more easily computerised because it does not depend on FHR baseline and individual deceleration identification.

Conclusions

The present study in fetal sheep, taken with previous large clinical cohort studies,[8-10, 13] support the concept that computerised metrics such as DA and DC could improve intrapartum FHR monitoring. Overall, DA and DC provide indices of cumulative exposure to intermittent moderate to severe fetal hypoxaemia. Potentially, the predictive value of DA and DC could be improved by using them in conjunction with other FHR features, but large human cohort studies suggest that DA or DC alone provide as good or better utility in predicting acidaemia as clinical assessment of all aspects of the FHR trace.[8-10] This strongly suggests that DA and DC capture information about intrapartum decelerations that is difficult to quantify in routine practice. Computerised DA and DC analysis of large, existing datasets can be used to objectively establish optimal thresholds relative to clinical risk factors and additional FHR metrics.[10, 48]

Disclosure of interests:

The authors have no conflicts of interest to declare.

Contribution to authorship:

AG, CAL, AJG and LB conceived the hypotheses and designed the study. CAL, JAW, MK and AJG undertook experimental work and data collection. AG and CAL performed data analysis and drafted the manuscript. CAL, AG, JAW, MK, EM, TI, AJG and LB contributed to interpreting data, editing and critically revising the manuscript, approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons who qualify for authorship are listed and all persons designated as authors qualify for authorship.

Details of ethics approval:

All procedures were approved by the Animal Ethics Committee of the University of Auckland (reference number 001942, approved 14/8/2017) following the New Zealand Animal Welfare Act 1999, and the Code of Ethical Conduct for animals in research established by the Ministry of Primary Industries, Government of New Zealand.

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530

Tables

Performance of DA (threshold 6500 bpm^2)			Performance of DC (threshold 9 bpm)				
MAP at threshold (mmHg)	**Time since first UCO (min)**	**Time till last UCO (min)**	**MAP at threshold (mmHg)**	**Time since first UCO (min)**	**Time till last UCO (min)**	**Final MAP (mmHg)**	**Total duration (min)**
1:5 UCOs							
-	-	-	-	-	-	45.3	240
-	-	-	-	-	-	42.8	240
-	-	-	-	-	-	49.2	240
-	-	-	-	-	-	39.0	240
-	-	-	-	-	-	35.5	240
-	-	-	-	-	-	38.5	240
1:2.5 UCOs							
61.6	75	155	59.1	65	165	22.7	220
46.4	50	160	45.8	65	145	21.1	200
45.8	70	85	51.8	85	70	20.8	145
35.3	35	115	36.0	30	120	21.8	140
41.2	85	140	37.7	100	125	22.4	215
45.5	205	90	26.8	260	35	22.2	285
54.8	80	60	35.9	110	30	17.6	130
-	-	-	-	-	-	43.5	235
38.3	30	55	42.7	20	65	19.2	75
33.3	90	80	43.8	15	155	20.9	160
50.2	30	150	50.6	15	165	20.0	170
-	-	-	-	-	-	31.2	235
Median (interquartile range)							
45.6 (38.3–50.2)	73 (35-85)	103 (80-150)	43.3 (36.0–50.6)	65 (20-100)	123 (65-155)		

Table 1. Performance of deceleration area and capacity

Each row represents individual values from each fetus in the 1:5 (n=6) and 1:2.5 groups (n=12). Cases that did not reach the threshold are indicated by dashes. DA, deceleration area; DC, deceleration capacity; MAP, mean arterial pressure; UCO, umbilical cord occlusion.

Figure legends

Figure 1: (A) Time course of changes in minimum mean arterial pressure, deceleration area and deceleration capacity during the umbilical cord occlusion (UCO) series. The data are displayed as four 20-minute epochs in order to account for the variable number of UCOs in individual experiments in the 1:2.5 group. Data are displayed as mean±SEM in the 1:5 (n=6) and 1:2.5 groups (n=12). *p<0.05 1:5 vs. 1:2.5-group. (B) Within-subjects relationships between minimum mean arterial pressure (min MAP) and deceleration area and deceleration capacity during the UCO series. (C) Within-subjects relationships between deceleration area and deceleration capacity during the UCO series. Individual data-points from all four epochs are displayed in (B) and (C).

Figure 2: Relationship of minimum mean arterial pressure with deceleration area and deceleration capacity during the umbilical cord occlusion series. Individual data-points are displayed from individual fetal sheep. The dashed lines indicate thresholds (deceleration area 6500 bpm^2, deceleration capacity 9 bpm) identified to provide early predictive of hypotension as detailed in Table 1.

Figure 3: (A) Time course of changes in deceleration amplitude during the umbilical cord occlusion (UCO) series. The data are displayed as four 20-minute epochs in order to account for the variable number of UCOs in individual experiments in the 1:2.5 group. Data are displayed as mean±SEM in the 1:5 (n=6) and 1:2.5 groups (n=12). *p<0.05, 1:5 vs. 1:2.5-group. (B) Within-subjects relationship between deceleration amplitude and the minimum mean arterial pressure (min MAP) during the UCO series. (C) Within-subjects relationships between deceleration amplitude and deceleration area (left panel) and deceleration capacity (right panel) during the UCO series. In (B) and (C), individual data-points from all four epochs are displayed.