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RESEARCH ARTICLE

Basic science

Fetal heart rate responses in chronic hypoxaemia with superimposed repeated hypoxaemia consistent with early labour: a controlled study in fetal sheep

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Abstract

Objective: Deceleration area (DA) and capacity (DC) of the fetal heart rate can help predict risk of intrapartum fetal compromise. However, their predictive value in higher risk pregnancies is unclear. We investigated whether they can predict the onset of hypotension during brief hypoxaemia repeated at a rate consistent with early labour in fetal sheep with pre-existing hypoxaemia.

Design: Prospective, controlled study.

Setting: Laboratory.

Sample: Chronically instrumented, unanaesthetised near-term fetal sheep.

Methods: One-minute complete umbilical cord occlusions (UCOs) were performed every 5 minutes in fetal sheep with baseline p_aO_2 <17 mmHg (hypoxaemic, $n = 8$) and >17 mmHg (normoxic, $n = 11$) for 4 hours or until arterial pressure fell <20 mmHg.

Main outcome measures: DA, DC and arterial pressure.

Results: Normoxic fetuses showed effective cardiovascular adaptation without hypotension and mild acidaemia (lowest arterial pressure 40.7 ± 2.8 mmHg, pH 7.35 ± 0.03). Hypoxaemic fetuses developed hypotension (lowest arterial pressure 20.8 ± 1.9 mmHg, $P < 0.001$) and acidaemia (final pH 7.07 ± 0.05). In hypoxaemic fetuses, decelerations showed faster falls in FHR over the first 40 seconds of UCOs but the final deceleration depth was not different to normoxic fetuses. DC was modestly higher in hypoxaemic fetuses during the penultimate ($P = 0.04$) and final ($P = 0.012$) 20 minutes of UCOs. DA was not different between groups.

Conclusion: Chronically hypoxaemic fetuses had early onset of cardiovascular compromise during labour-like brief repeated UCOs. DA was unable to identify developing hypotension in this setting, while DC only showed modest differences between groups. These findings highlight that DA and DC thresholds need to be adjusted for antenatal risk factors, potentially limiting their clinical utility.

KEYWORDS
asphyxia, cardiotocography, computerised fetal heart rate monitoring, deceleration area, deceleration capacity, hypotension, hypoxia-ischaemia, mortality, peripheral chemoreflex, phase rectified signal averaging, stillbirth

Christopher A. Lear and Antoniya Georgieva are joint first authors.

1 | INTRODUCTION

Cardiotocography (CTG) monitoring during labour shows poor ability to predict fetal acidaemia or hypoxia-ischaemia, and reliable indices of fetal wellbeing are needed.[1–7] Recent studies suggest that deceleration area (DA) and deceleration-related metrics such as deceleration capacity (DC) may be more effective predictors than standard clinical assessment.[8–17] These indices quantify the total burden of decelerations including depth, duration and frequency.

Deceleration area predicted neonatal acidaemia in large retrospective[8] and prospective cohorts.[9] Further, DA was more predictive of acidaemia than fetal heart rate (FHR) variability or numbers of late decelerations,[14] and of neonatal encephalopathy in recent retrospective cohort studies.[16] The computational index DC predicted both fetal acidaemia and neonatal compromise in a cohort of 22 790 births[10] and predicted acidaemia better than short-term variation.[13] DC is derived from a modern signal processing technique called phase rectified signal averaging, which was originally described in the setting of myocardial infarction in adults[18] but is easily adapted to quantify FHR decelerations.[10,13,19] The reader should note that the term 'capacity' should not be taken literally. DC is simply a measure of the mean fall in FHR over a given period and provides a combined measure of the frequency and speed of decelerations, and time spent at or away from FHR baseline.

In recent animal studies, DA and DC predicted fetal hypotension[19] and acidemia.[19–21] Hypotension is the key determinant of neural injury[22–24] and therefore its relation with hypotension[19] provides physiological support for the utility of DA and DC. Their practical implementation requires defined thresholds for intervention. Georgieva and colleagues found that risk factors including pre-eclampsia and thick meconium reduced the DC threshold associated with intrapartum compromise,[10] emphasising that computerised metrics should be adapted to the clinical context, similarly to visual CTG interpretation.[25,26]

In the present study we examined the FHR response of near-term fetal sheep with pre-existing (chronic) hypoxaemia exposed to acute hypoxaemia induced by complete, brief umbilical cord occlusions (UCOs)[27–31] repeated at a frequency consistent with contractions in early labour.[32] We assessed the morphology of decelerations including the amplitude of decelerations and the ability of DA and DC to detect the development of arterial hypotension, to test the hypothesis that fetuses with pre-existing hypoxaemia would develop hypotension at lower values of DA and DC compared with normoxic fetal sheep.

2 | METHODS

2.1 | Ethics and surgery

All procedures were approved by the Animal Ethics Committee of the University of Auckland (number 22069) following the New Zealand Animal Welfare Act and comply with the ARRIVE guidelines.[33] A total of 19 Romney/Suffolk fetal sheep were surgically instrumented at 116–122 days' gestation.[34,35] Ewes received oxytetracycline (20 mg/kg; Phoenix Pharm Distributors) intramuscularly for antibiotic prophylaxis. Anaesthesia was induced with propofol (5 mg/kg; AstraZeneca) and maintained using 2–3% isoflurane in oxygen. Fetuses were partially exteriorised via a midline abdominal incision and uterotomy. Catheters were placed in the femoral artery to measure mean arterial pressure (MAP), brachial artery for preductal blood sampling and amniotic sac to correct for maternal position. Electrodes (AS633-5SSF; Cooner Wire) were placed across the fetal chest to measure the electrocardiogram. An inflatable umbilical cord occluder was placed (In Vivo Metric).

Fetuses were returned to the uterus, gentamicin was administered into the amniotic sac (80 mg; Pfizer), and uterotomy and abdominal incisions were closed. The maternal midline skin incision was infiltrated with long-acting local analgesic (0.5% bupivacaine plus adrenaline, AstraZeneca). Fetal leads were exteriorised through the maternal flank and a maternal long saphenous vein was catheterised.

2.2 | Postoperative care and signal acquisition

After recovering from anaesthesia, ewes were housed together in metabolic cages with ad libitum access to food and water, in environmentally controlled rooms (16 ± 1°C, humidity 50 ± 10%, 12-hour light/dark cycle). Ewes received intravenous antibiotics for 4 days (80 mg gentamicin, 600 mg benzylpenicillin-sodium; Novartis). Fetal leads were connected to signal acquisition hardware and all signals were recorded continuously using LabVIEW-based software (National Instruments).[34] Fetal blood pressures were recorded using Novatrans III, MX860 Gold transducers (Medex).

2.3 | Experimental protocol

Experiments were conducted 4–5 days after surgical instrumentation to allow fetuses to completely recover from anaesthetics. Fetuses with stable P_aO_2 <17 mmHg for ≥3 days were assigned to the pre-existing hypoxaemia group (n = 8), representing the 5th percentile in healthy term singleton fetuses. Fetuses with P_aO_2 ≥17 mmHg were assigned to the normoxic group (n = 11).

Umbilical cord occlusions were performed at 124.8 ± 0.7 days' gestation (term gestation 147 days), when sheep neural development approximates term humans.[36] Umbilical cord occluders were rapidly inflated with a volume of saline known to cause complete UCO for 1 minute before the occluder was deflated for 4 minutes of reperfusion. UCOs were repeated at this rate for 4 hours (total 49 UCOs) or until MAP reached <20 mmHg on two successive UCOs. This occlusion frequency is consistent with the frequency of uterine contractions during early first stage of labour (2 per 10 minutes).[28,31,37]

Arterial samples (0.3 ml) were collected before experiments, after every 12th UCO and the final UCO to measure pH, blood gases, oximetry (ABL800-Basic; Radiometer), glucose and lactate concentrations (YSI-2300). Animals were killed 72 hours after experiments by pentobarbital-sodium overdose intravenously to the ewe (9 g; Chemstock International).

2.4 | Data extraction and time-points

Continuous 1-second means of FHR and MAP were extracted (LabVIEW, National Instruments). Baseline was defined as the 60 minutes before UCOs. Four 20-minute epochs each containing four UCOs were examined (the first, middle, penultimate and final 20 minutes of UCOs) in order to account for the unequal duration of individual experiments in the hypoxaemic group, as endpoints were reached at different times. During each epoch, we assessed the change in FHR and MAP during and between UCOs and the morphology of decelerations by calculating changes in FHR relative to the immediate baseline (i.e. interocclusion FHR immediately before each UCO). For display purposes, changes relative to interocclusion FHR were averaged across the four UCOs in each epoch.

2.5 | Deceleration area and capacity

DA and DC were calculated using the Oxford System for Intrapartum FHR Analysis.[38–40] The algorithms to detect baseline and decelerations are based on signal processing methods optimised to fit expert evaluation of intrapartum CTGs.[41,42] DA and DC were calculated as the average of two overlapping 15-minute epochs, separated by a 5-minute step. Windows therefore overlap by 10 minutes, spanning 20 minutes. DC was calculated as previously described,[10,38] from the phase-rectified signal averaging algorithm ($T = 1$, $L = 11$ for data sampled at 1 Hz),[18] which interrogates repeating fluctuations between successive heart rate measurements.

DA was calculated as the sum of deceleration areas in each epoch, estimated as (duration × depth)/2.[9] DA was also calculated over 120 minutes. The maximum DC reached during the UCO series was calculated to mirror clinical studies.[9,18] A more precise measure of DA was also calculated as the sum of the relative fall in FHR during UCOs. Additionally, we calculated the absolute FHR at 30 seconds of UCO, the maximal relative fall in FHR during UCO (deceleration amplitude), the lowest FHR during UCO (deceleration nadir) and the maximal absolute FHR reached within the first 90 seconds after UCO (overshoot tachycardia).

2.6 | Statistics

Data were analysed using SPSSv28 (IBM). Changes during UCOs were evaluated by repeated measures analysis of variance (ANOVA), with group, epoch and the four UCOs within each epoch treated as independent factors and time as a repeated factor. Six time epochs were investigated separately: the first, middle and last 20 seconds during UCOs and four reperfusion minutes between UCOs. If interactions between epoch and group were found, repeated measures ANOVA on each epoch was performed. Changes in FHR metrics were assessed by two-way ANOVA, with epochs treated as repeated measures. Individual epochs were compared by one-way ANOVA if an overall effect was observed. Biochemical data were compared between groups by two-way ANOVA, with time treated as a repeated measure. Data are means ± SEM. Statistical significance was accepted when $P < 0.05$.

3 | RESULTS

3.1 | Group characteristics

The normoxic group included six females, four males, one unrecorded sex, seven singletons and four twins (postmortem body weight 4.03 ± 0.14 kg). The hypoxaemic group included three females, five males, one singleton, five twins, two triplets (postmortem bodyweight 3.27 ± 0.23 kg, $P = 0.005$ versus normoxic). Mild metabolic acidaemia developed in the normoxic group compared with severe metabolic acidaemia in the hypoxaemic group (Table 1).

3.2 | Arterial pressure

All fetuses in the normoxic group received the full 49 UCOs over 4 hours while maintaining cardiovascular stability. The lowest MAP recorded was 40.7 ± 2.8 mmHg at the end of experiment (Figure 1). All fetuses in the hypoxaemic group developed severe hypotension. On average, hypoxaemic fetuses received 44.8 ± 2.0 UCOs (lowest MAP 20.8 ± 1.9 mmHg). Experiments were ended early in 4/8 fetuses (40.5 ± 2.5 UCOs, lowest MAP 17.1 ± 1.6 mmHg) and 4/8 fetuses completed 49 UCOs (lowest MAP 24.5 ± 2.4 mmHg).

MAP was lower in hypoxaemic fetuses during the last 40 seconds of UCOs in the middle (21–40 seconds, $P = 0.014$; 41–60 seconds, $P < 0.001$), penultimate ($P < 0.001$, $P < 0.001$) and final 20-minute epochs ($P < 0.001$, $P < 0.001$). Between occlusions, MAP was initially higher in hypoxaemic fetuses during the first reperfusion minute in the first 20-minute epoch ($P = 0.002$) but subsequently was lower during the first reperfusion minute in the penultimate 20-minute epoch ($P = 0.002$) and first and second reperfusion minutes in the final 20-minute epoch ($P < 0.001$, $P = 0.007$). In one normoxic fetus, continuous MAP was partially lost, but on 1-minute mean data, final MAP was 58.7 mmHg.

3.3 | Fetal heart rate

UCOs were associated with rapid FHR decelerations in both groups (Figure 1). During the first 40 sconds of UCOs, FHR was lower in hypoxaemic fetuses in the middle ($P = 0.022$,

TABLE 1 Fetal pH, blood gases and metabolites.

	Baseline	First 30 minutes	Middle 30 minutes	Final 30 minutes
pH				
Normoxic	7.42 ± 0.01	7.36 ± 0.02	7.34 ± 0.02	7.35 ± 0.03
Hypoxaemic	7.37 ± 0.01*	7.19 ± 0.02*	7.09 ± 0.04*	7.07 ± 0.05*
P_aCO_2 (mmHg)				
Normoxic	46.0 ± 1.1	48.2 ± 3.1	45.3 ± 3.0	46.8 ± 1.9
Hypoxaemic	50.2 ± 1.3*	58.9 ± 2.2*	53.9 ± 2.1*	54.2 ± 3.4
P_aO_2 (mmHg)				
Normoxic	22.1 ± 0.6	18.8 ± 0.8	20.0 ± 0.6	16.7 ± 0.6
Hypoxaemic	11.4 ± 0.9*	13.8 ± 0.7*	15.3 ± 0.7*	14.4 ± 1.2
Hb (g/dl)				
Normoxic	11.0 ± 0.5	11.4 ± 0.5	11.0 ± 0.5	11.1 ± 0.5
Hypoxaemic	10.9 ± 0.7	11.7 ± 0.8	10.8 ± 0.7	11.2 ± 0.6
Hct (%)				
Normoxic	32.4 ± 1.5	33.3 ± 1.3	33.6 ± 1.5	32.6 ± 1.4
Hypoxaemic	32.3 ± 2.0	34.5 ± 2.3	31.9 ± 2.0	33.0 ± 1.9
ctO_2 (mmol/l)				
Normoxic	4.5 ± 0.3	3.4 ± 0.2	3.4 ± 0.3	3.0 ± 0.2
Hypoxaemic	1.8 ± 0.3*	2.0 ± 0.3*	1.6 ± 0.2*	1.5 ± 0.2*
S_aO_2 (%)				
Normoxic	67.6 ± 1.3	49.0 ± 3.8	51.0 ± 3.5	43.0 ± 1.7
Hypoxaemic	27.5 ± 3.6*	28.8 ± 3.9*	24.9 ± 2.3*	22.4 ± 2.2*
BE (mmol/l)				
Normoxic	4.0 ± 0.9	−0.4 ± 1.4	−2.0 ± 1.6	−0.5 ± 1.3
Hypoxaemic	2.4 ± 0.7	−6.2 ± 1.2*	−13.2 ± 1.4*	−14.5 ± 1.7*
Lactate (mmol/l)				
Normoxic	1.2 ± 0.2	2.7 ± 0.7	4.0 ± 1.3	4.7 ± 1.6
Hypoxaemic	2.5 ± 0.6	6.3 ± 1.1*	11.2 ± 1.7*	12.2 ± 2.3*
Glucose (mmol/l)				
Normoxic	0.8 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	1.0 ± 0.2
Hypoxaemic	0.7 ± 0.1	1.3 ± 0.2	1.2 ± 0.1	1.1 ± 0.2

Abbreviations: BE, base excess; ctO_2, arterial oxygen content; Hb, haemoglobin concentration; Hct, haematocrit; P_aCO_2, arterial pressure of carbon dioxide; P_aO_2, arterial pressure of oxygen; S_aO_2, arterial oxygen saturation.

*$P < 0.05$ normoxic versus hypoxaemic.

$P = 0.002$), penultimate ($P = 0.026$, $P = 0.002$) and final 20-minute epochs ($P = 0.024$, $P = 0.001$). During the final 20 seconds of UCOs, FHR was lower in hypoxaemic fetuses during the middle 20 minutes compared with the normoxic group ($P = 0.019$). During reperfusion, interocclusion FHR was higher in hypoxaemic fetuses for the first minute after UCO in the first ($P = 0.014$) and middle 20-minute epochs ($P = 0.013$). The evolution of changes in the FHR response is shown in Figure 2A.

3.4 | Deceleration morphology

The rate fall in FHR was greater in hypoxaemic fetuses in the first 40 seconds of UCOs in all 20-minute epochs ($P < 0.001$, $P = 0.001$, Figure 2B), but not in the final 20 seconds of UCOs. Relative to the same interocclusion FHR, there was a greater relative increase in FHR between 15 and 35 seconds during the reperfusion period in the hypoxaemic group across all epochs ($P = 0.041$). The evolution of deceleration morphology is shown in Figure 2C.

There was no difference between groups in either the amplitude ($P = 0.296$) or nadir of decelerations across the experiment ($P = 0.466$, Figure 3). The maximal absolute FHR reached during the first 90 seconds of reperfusion (overshoot tachycardia) was greater in hypoxaemic fetuses during the first ($P = 0.004$), middle ($P < 0.001$) and penultimate epochs ($P = 0.03$).

3.5 | Deceleration area and capacity

There was an overall effect of group on DC across all epochs ($P = 0.029$, Figure 3), such that DC was borderline higher in hypoxaemic fetuses in the first ($P = 0.051$) and significantly higher in the penultimate ($P = 0.04$) and final epochs ($P = 0.012$). There was an effect of group on max-DC ($P = 0.023$), such that max-DC was borderline higher in hypoxaemic fetuses in the first ($P = 0.053$), and significantly higher in the middle ($P = 0.021$), penultimate ($P = 0.019$) and final epochs ($P = 0.016$). There was no difference between groups in DA when calculated over 20 minutes ($P = 0.512$, Figure 3) or 120 minutes ($P = 0.313$, data not shown), or as the sum of the relative falls in FHR during decelerations ($P = 0.478$, data not shown).

3.6 | Correlations with deceleration capacity and hypotension

Changes in DC were associated with the magnitude of overshoot tachycardia after decelerations in the first ($P < 0.001$, $R^2 = 0.61$, $n = 19$), penultimate ($P < 0.001$, $R^2 = 0.49$, $n = 19$) and final epochs ($P < 0.001$, $R^2 = 0.51$, $n = 19$). DC was not associated with the fall in FHR at 20, 30 or 40 seconds during UCOs, nor the final amplitude or nadir of the decelerations (data not shown).

DC was associated with min-MAP during the penultimate ($P = 0.002$, $R^2 = 0.44$, $n = 19$) and final epochs ($P = 0.009$, $R^2 = 0.34$, $n = 19$, Figure 3C). Min-MAP was associated with the magnitude of overshoot tachycardia during the middle ($P = 0.007$, $R^2 = 0.49$, $n = 19$, Figure 1B) and penultimate epochs ($P = 0.02$, $R^2 = 0.28$, $n = 19$), and statistically borderline in the final epoch ($P = 0.051$). Min-MAP was associated with FHR at 30 seconds of UCOs during the middle ($P < 0.001$, $R^2 = 0.36$, $n = 19$, Figure 1B), penultimate ($P = 0.015$, $R^2 = 0.31$, $n = 19$) and final epochs ($P = 0.006$, $R^2 = 0.36$, $n = 19$). There was no relation between min-MAP and either deceleration amplitude or nadir (data not shown).

4 | DISCUSSION

4.1 | Main findings

We examined the FHR response in fetal sheep with chronic spontaneous hypoxaemia subjected to brief repeated hypoxaemia at a rate consistent with early labour (2 per 10 minutes).

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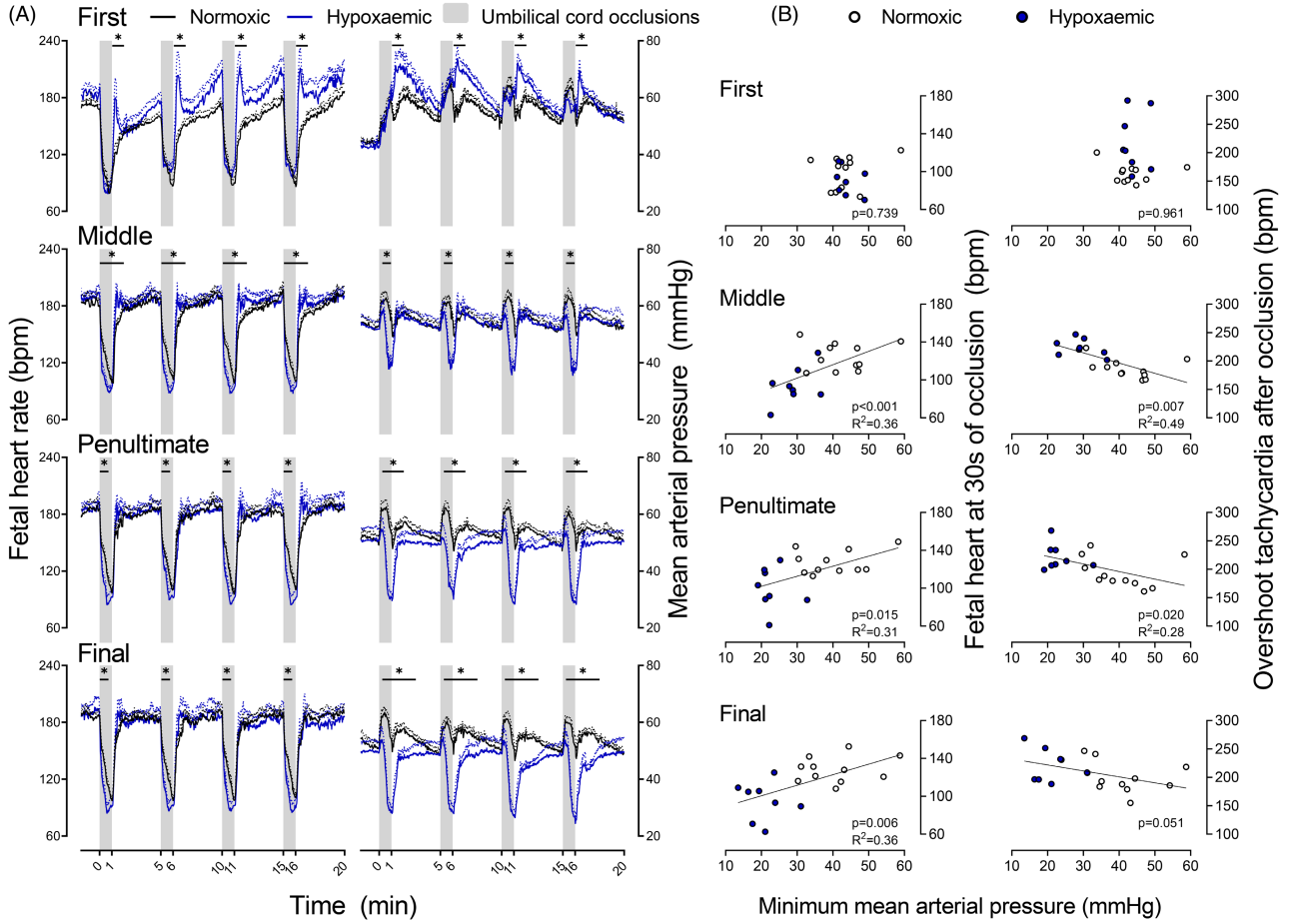

FIGURE 1 Fetal heart rate and mean arterial pressure during repeated umbilical cord occlusions. (A) Time course of changes in fetal heart rate (first column) and arterial pressure (second column) across the four epochs assessed (shown sequentially down the columns). The normoxic group is shown in black ($n = 11$), the hypoxaemic group in blue ($n = 8$) and the periods of UCOs in grey shading. *$P < 0.05$ normoxic versus hypoxaemic. Data are 1-second means ± SEM, dotted lines represent SEM. (B) Relation between minimum mean arterial pressure recorded in each epoch and either fetal heart rate at 30 seconds of occlusion (third column) or the maximum magnitude of overshoot tachycardia after occlusion (fourth column). The four epochs assessed are shown sequentially down the columns. Overshoot tachycardia was calculated as the highest absolute fetal heart rate during the first 90 seconds after the end of occlusions. Each datapoint represents the average of the four occlusions included in each epoch from individual fetuses.

This study shows that higher DC but not DA was associated with lower MAP during the penultimate and final epochs, but these changes were modest, with substantial overlap between groups. Overall, DA and DC showed limited ability to identify evolving hypotension in the present study. This contrasts with healthy normoxic foetuses, which showed a progressive increase in DA and DC after the onset of cardiovascular compromise.[19]

The hypoxaemic group had an average p_aO_2 of 11.4 ± 0.9 mmHg and S_aO_2 of 27.5 ± 3.6% before UCOs (versus 22.1 ± 0.1 mmHg and S_aO_2 67.6 ± 1.3% in normoxic fetuses), and reduced bodyweight, consistent with fetal growth restriction.[31,43,44] Normoxic fetuses tolerated repeated UCOs without hypotension and only mild acidaemia. Hypoxaemic fetuses maintained arterial pressure during the first epoch but thereafter showed impaired cardiovascular adaptation with progressively worse hypotension during UCOs.[45–47] This likely reflects failing ventricular output[48] secondary to depletion of myocardial glycogen stores, intracellular acidosis and potentially evolving myocardial injury.[30,49,50]

Throughout the experiment, FHR fell faster during decelerations in the hypoxaemic group, with a greater relative fall in FHR during the first 40 seconds of UCOs, but no difference in the maximal depth of decelerations in the final 20 seconds. This initial fall in FHR during decelerations is mediated by the peripheral chemoreflex,[34] followed by an increasing contribution of the negative chronotropic effects of myocardial hypoxia that sustains decelerations.[48] The greater initial fall in FHR therefore likely reflects augmented peripheral chemoreflex activation.[34] Itskovitz and colleagues reported a very similar pattern of faster and deeper decelerations during nearly complete 20-second uterine artery occlusion in hypoxaemic near-term fetal sheep.[51] In the present study, the fall in FHR was greater in hypoxaemic fetuses from 20 to 40 seconds during UCOs, and thus it is likely that decelerations would have been deeper during similarly short UCOs. Thus, these studies strongly suggest that pre-existing hypoxaemia will be associated with faster (and potentially deeper) decelerations during human intrapartum contractions whether hypoxaemia was secondary to UCO

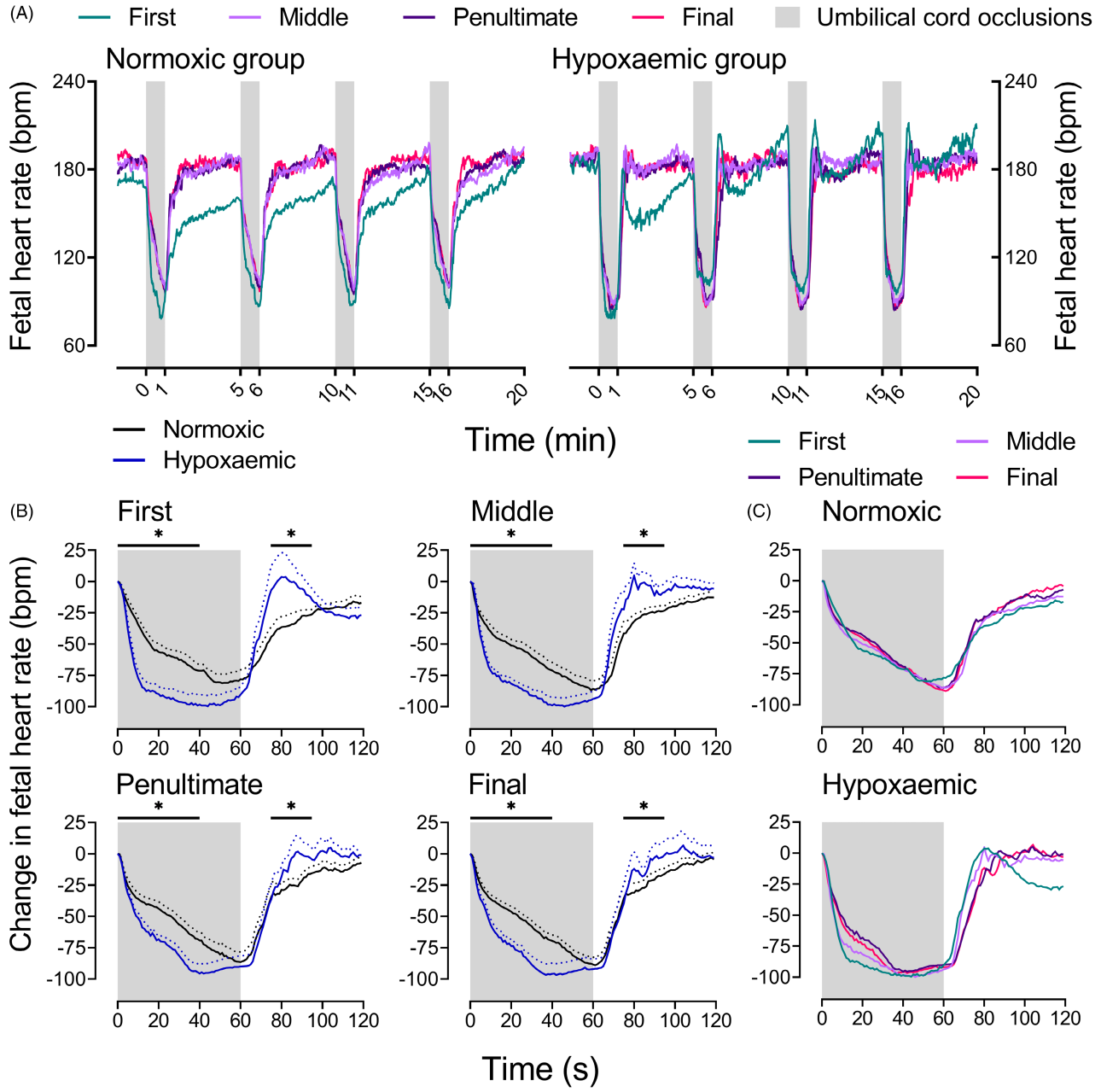

FIGURE 2 Evolution of fetal heart rate changes during repeated umbilical cord occlusions. (A) Fetal heart rate from the four epochs superimposed on each group to allow assessment of the changes over time. The data displayed are 1-second means from each epoch. The data is the same as displayed in Figure 1 without SEM. (B) Morphology of decelerations assessed relative to the immediate baseline before the start of each occlusion in the normoxic (black, $n = 11$) and hypoxaemic groups (blue, $n = 8$). Data displayed are the average of the four occlusions in each epoch. $^*P < 0.05$ normoxic versus hypoxaemic. Data are 1-second means ± SEM, dotted lines represent SEM. (C) The data displayed in (B) has been superimposed without SEM on each group to allow assessment of the evolution of deceleration morphology throughout the experiment.

or utero-placental compression. In contrast, a recent report found slowing of FHR decelerations in fetal sheep with mild chronic hypoxaemia.[21] This difference likely in part reflects the use of initial partial rather than complete UCOs and milder pre-existing hypoxaemia (defined as baseline S_aO_2 <55%, versus mean 27.5 ± 3.6% in the present study).[21]

In the present study, the morphology of decelerations in the hypoxaemic group visually appear to be more 'U-shaped' than the 'V-shape' in the normoxic group. Of interest, lower FHR at 30 seonds of UCO correlated with min-MAP (Figure 1B), suggesting that cardiovascular compromise is associated with faster decelerations even if the final nadir is not different.[44] Despite the apparent greater area of individual decelerations, there were only modest differences in DC between the groups and no difference in DA. There was also no difference between groups for DA calculated over 120 minutes,[9] or as the sum of the relative falls in FHR throughout each deceleration.

The late, modest increase in DC in the penultimate and final 20 minutes developed after fetuses had already developed severe hypotension. We have previously reported that seizure

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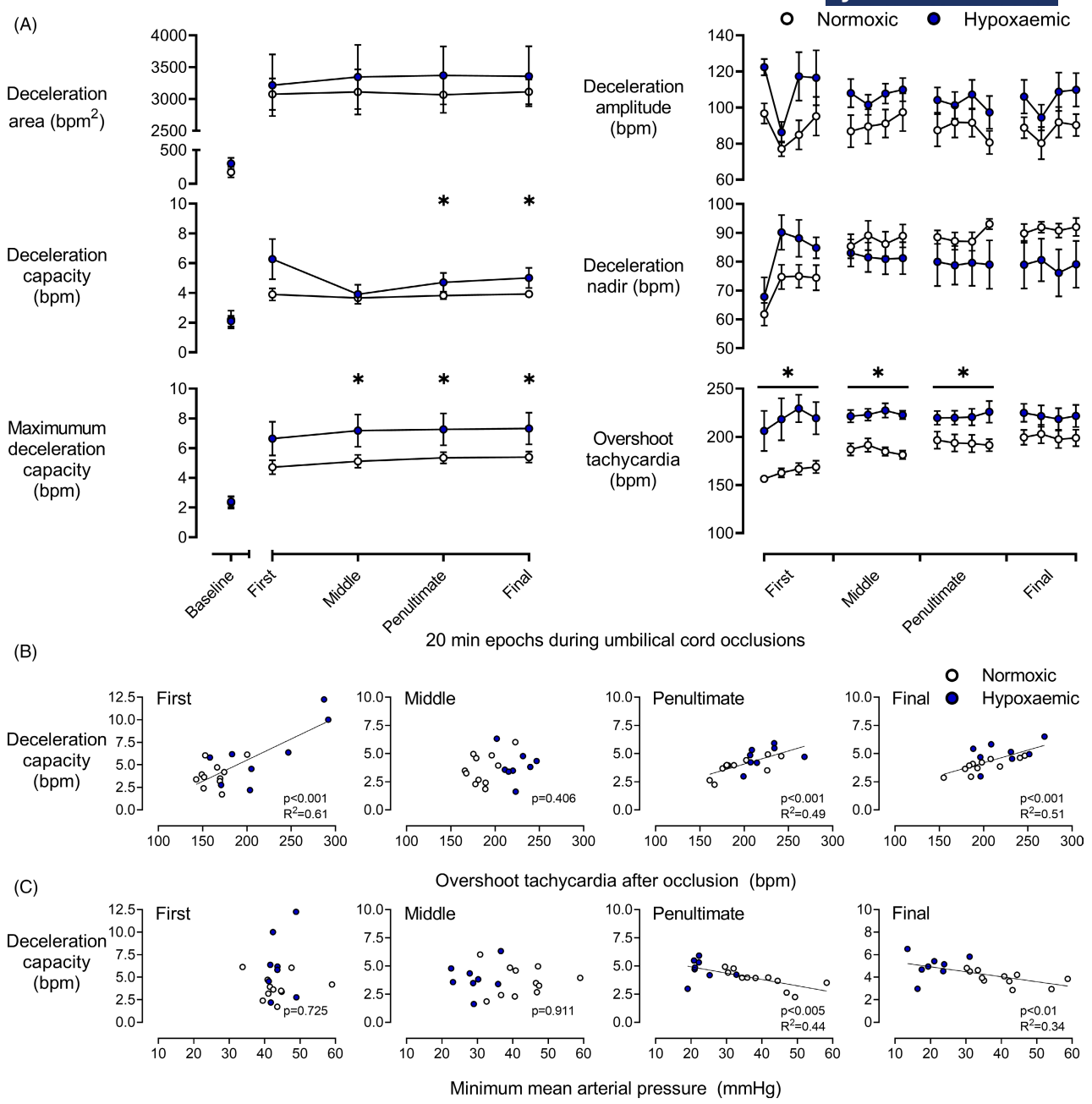

FIGURE 3 Fetal heart rate metrics and associations with hypotension during repeated umbilical cord occlusion. (A) Fetal heart rate (FHR) metrics in the normoxic (white, $n = 11$) and hypoxaemic groups (blue, $n = 8$). Maximum deceleration capacity represents the maximal value identified. Deceleration amplitude was calculated as the maximal relative fall from baseline immediately before each occlusion. Deceleration nadir represents the lowest FHR reached during occlusion. Overshoot tachycardia was calculated as the highest absolute fetal heart rate during the first 90 seconds after the end of occlusions. Data are mean ± SEM. *$P < 0.05$ normoxic versus hypoxaemic. (B) Relation between deceleration capacity and the magnitude of overshoot tachycardia after each occlusion across the four epochs. (C) Relation between deceleration capacity and minimum mean arterial pressure identified during occlusions across the four epochs. (B,C) Each datapoint represents the average of the four occlusions included in each epoch from individual fetuses.

activity (on electroencephalographic monitoring) developed in chronically hypoxaemic fetuses during repeated UCOs, at a mean of 148 ± 45 minutes after the start of UCOs,[45] supporting that injury was already present at this time. Expedited delivery at this late stage is therefore unlikely to completely prevent injury, although potentially it might mitigate further injury and allow earlier recruitment for neuroprotective therapy if appropriate.[52] This represents an important limitation of these metrics and emphasises that lower thresholds for either DA or DC would need to be adopted when antenatal risk factors are present. The mean DC at these times were 4.7 and 5.0 bpm, compared with the DC threshold of 4.0 bpm suggested in human labours with risk factors such as thick meconium and pre-eclampsia.[10] Previous studies strongly support the concept that including clinical risk factors can improve the predictive value of FHR patterns.[25,26]

Overall, the poor performance of DA and DC is disappointing considering that both measures progressively increased with worsening hypotension in well-grown normoxic fetuses exposed to more frequent UCOs (4 per 10 minutes), reflecting deepening decelerations.[19] In the present study, decelerations did not deepen with progressive hypotension, suggesting that fetuses with chronic antenatal hypoxaemia can become compromised without significant change in their FHR pattern, although their decelerations were faster throughout the experiment. This difference may reflect longer reperfusion between UCOs allowing greater resolution of myocardial hypoxia.[48,53] If this was the case, it was insufficient to help sustain combined ventricular output. Further studies are needed to determine whether frequent UCOs in fetuses with pre-existing hypoxaemia are associated with greater differences in responses to normoxic fetuses.

Nonetheless, DC was still correlated with MAP across both groups in the penultimate and final epochs in the present study. This phase of increased DC appeared to be predominantly mediated by overshoot tachycardia after decelerations.[54,55] Overshoot tachycardia also correlated with MAP, whereas the nadir of decelerations did not. Overshoot tachycardia is mediated by the combination of impaired parasympathetic tone and high circulating catecholamines,[54,55] suggesting that hypoxaemic fetuses developed earlier loss of parasympathetic tone during UCOs. Thus, DC is sensitive to multiple features of the FHR trace and in some settings may be superior to DA in predicting fetal compromise.

A limitation of the present study is that hypoxaemic fetuses had a high rate of cardiovascular instability after UCOs, with early mortality, consistent with substantial multi-organ injury, and so we could not assess histological brain injury. Nonetheless, hypotension is highly associated with the severity of hypoxic–ischaemic injury across multiple experimental paradigms.[22–24] We have previously reported that a similar degree of hypotension to the present study was associated with cytotoxic cerebral oedema, cortical and subcortical neuronal death[27] and subendocardial injury.[30] Further, chronic hypoxaemia was associated with early onset of seizures and delayed recovery of sleep state cycling during repeated UCOs,[45] consistent with neural injury.[27] Of interest, the ultimate severity of acidaemia in the present study (7.09 ± 0.04) was less than in our previous study of more frequent occlusions in normoxic fetuses (6.84 ± 0.11).[27] This emphasises that fetuses with antenatal risk factors may become hypotensive and develop significant neural injury despite relatively modest acidaemia.

In the present study, there was a trend to increased DC in the hypoxaemic group during the first epoch that appeared to be related to marked overshoot tachycardia in a subset of the hypoxemic fetuses (Figure 3C). The sustained increase in max-DC throughout the experiment mainly reflected this early increase. A clinical study has reported that an early increase in DC that resolved in later labour was still associated with increased risk of fetal compromise.[10] Moreover, in a case–control study of 220 singleton births, labour augmentation with syntocinon was associated with an early, transient increase in DC among fetuses who later developed acidaemia, despite no increase in the number of decelerations.[56] Overall, these clinical and preclinical findings raise the possibility that an increase in DC in early labour may offer an early warning of greater risk of compromise.

4.2 | Strengths and limitations

The strength of present study is the ability to simultaneous assess the relation between FHR metrics and arterial blood pressure, whereas clinical studies need to use surrogate measures such as pH, or rare outcomes such as hypoxic-ischaemic encephalopathy. We allowed full recovery from anaesthesia, which impairs the cardiovascular responses to hypoxaemia.[57] This study utilised a highly structured protocol of complete UCOs, consistent with the frequency of contractions in first stage labour of approximately 2 per 10 minutes,[32] but this of course cannot capture the heterogeneity of human labour. The pattern of progressively evolving hypoxaemia examined in the present study represents only one pathway leading to hypoxic-ischaemic encephalopathy. Nevertheless, the present findings are likely to be relevant to evolving intrapartum hypoxia-ischaemia in humans.

5 | CONCLUSIONS

This study suggests that lower DA and DC thresholds in labours will be needed when there are antenatal risk factors,[10] emphasising that even computerised assessment needs to incorporate the clinical context. This likely reflects that both DA and DC predominantly provide an index of the cumulative exposure to hypoxaemia, rather than direct information on fetal adaptation at any one time.[19] Nonetheless, DA and DC remain promising, objective predictors for intrapartum compromise.[8–10,14,16,17,58] Additional biomarkers may help improve their utility. For example, we have previously shown that hypoxaemic fetuses developed a significantly greater rise in T/QRS ratio during repeated UCOs,[47] suggesting that it may be complementary to DA and/or DC.

Finally, the clinical application of DA or DC relies on real-time computerised FHR analysis. DA has been studied for decades.[9,59,60] Although less intuitive, DC has the advantage that it can be easily incorporated into automated computerised systems. First, the underlying algorithm is very tolerant of noise within the CTG signal. Secondly, DC is a standalone algorithm, whereas DA needs to be measured as part of a complex system that accurately identifies baseline FHR and both the start and end of decelerations. Thirdly, DC is sensitive to multiple aspects of the FHR trace that may indicate risk. In a previous study DC was sensitive to deeper decelerations,[19] and in the present study to overshoot tachycardia. Thus, DC may have somewhat greater pragmatic utility.

AUTHOR CONTRIBUTIONS

These experiments were designed and conducted in the Fetal Physiology and Neuroscience Group laboratory, at

the University of Auckland. CAL, LB, AG and AJG conceived the hypotheses and design for this study. CAL, GW, SKD, BAL, OJM, JAW, LB and AJG were responsible for all experimental work and data collection. CAL and AG performed the data analysis and drafted the paper. All authors were involved in data interpretation and critically reviewed the paper. All authors listed qualify for authorship and approved the final version of the paper. CAL and AG contributed equally to this article and qualify as joint first authors.

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CONFLICT OF INTEREST STATEMENT

None declared. Completed disclosure of interest forms are available to view online as supporting information.

DATA AVAILABILITY STATEMENT

The data are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

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