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ORIGINAL RESEARCH

Atrioventricular conduction abnormalities are associated with poor outcome following intermittent umbilical cord occlusions in fetal sheep

Juulia Lantto[1] | Jonas Johnson[1] | Heikki Huhta[2] | Mervi Haapsamo[3] | Panu Kiviranta[4,5] | Kati Räsänen[4] | Hanna-Marja Voipio[6] | Sven-Erik Sonesson[7] | Juha Voipio[8] | Juha Räsänen[9] | Ganesh Acharya[1]

[1]Division of Obstetrics & Gynecology, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, Stockholm, Sweden

[2]Translational Research Group, Oulu University Hospital and Oulu University, Oulu, Finland

[3]Felicitas-Mehiläinen, Gynecological and Infertility Clinic, Oulu, Finland

[4]Kuopio Pediatric Research Unit, University of Eastern Finland & Kuopio University Hospital, Kuopio, Finland

[5]The Finnish Medical Society Duodecim, Helsinki, Finland

[6]Oulu Laboratory Animal Centre, Oulu University Hospital and Oulu University, Oulu, Finland

[7]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

[8]Faculty of Biological and Environmental Sciences, Molecular and Integrative Biosciences Research Program, University of Helsinki, Helsinki, Finland

[9]Helsinki University Hospital and University of Helsinki, Helsinki, Finland

Correspondence
Ganesh Acharya, Division of Obstetrics & Gynecology, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, 14186 Stockholm, Sweden.
Email: ganesh.acharya@ki.se

Abstract

Introduction: Fetal arrhythmias have been described with intrapartum hypoxemia; however, they cannot be accurately diagnosed with currently used fetal heart rate (FHR) monitoring systems due to low resolution and signal averaging. We used a Holter device to record electrocardiogram (ECG) at 250 Hz in term sheep fetuses that developed severe metabolic acidosis induced by intermittent umbilical cord occlusions (UCOs), mimicking human labor contractions. We hypothesized that UCOs leading to worsening fetal metabolic acidosis provoke distinct fetal arrhythmias that could indicate impending fetal death.

Material and Methods: Thirteen pregnant sheep (gestational age 133–135/145 days) were instrumented under general anesthesia. Three electrodes were placed on the fetal chest and connected to a Holter device for continuous ECG recording at a sampling rate of 250 Hz. The fetal axillary artery was catheterized and an inflatable occluder was placed around the umbilical cord. After a 4–5 day recovery, complete UCOs were induced by inflating the occluder for 1 min, followed by deflation for 2 min, until the fetal arterial pH dropped <7.0 and/or base excess (BE) <−16. Thereafter, an emergency cesarean section was performed to deliver the fetus.

Results: Eight sheep fetuses were included in the final analysis. All fetuses had normal baseline arterial blood gases and lactate values. During the first two UCOs, all fetuses demonstrated isolated benign arrhythmias. Three fetuses that developed severe metabolic acidosis after five UCOs showed persistent atrioventricular (AV) conduction abnormalities during the last UCO and its release, requiring cardiopulmonary resuscitation (CPR) at birth. One fetus with third-degree AV block had no detectable QRS complexes at birth, developed ventricular tachycardia and fibrillation (VT/VF) during CPR, and was successfully defibrillated. Five fetuses tolerated ≥10 UCOs before

Abbreviations: AV, atrioventricular; ECG, electrocardiography; SA, sinoatrial; UCO, umbilical cord occlusions; VF, ventricular fibrillation; VT, ventricular tachycardia.

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developing severe metabolic acidosis, and none of these showed any persistent AV-conduction abnormalities, though one fetus died after developing VT/VF after the 10th UCO.

Conclusions: Metabolic acidemia induced by intermittent UCOs in term sheep fetuses is associated with various arrhythmias, some of which may be life-threatening. Continuous intrapartum fetal ECG recording at a sample rate of ≥250 Hz coupled with a software capable of automatically detecting significant arrhythmias could enhance intrapartum fetal monitoring in the future.

KEYWORDS
arrhythmia, electrocardiography, fetal monitoring, Holter, hypoxia, metabolic acidosis, sheep

1 | INTRODUCTION

Monitoring of fetal well-being in labor is commonly based on fetal heart rate (FHR) tracing obtained by cardiotocography (CTG) that is a continuous wave Doppler-based technique with a low sampling rate (≈4 Hz). It does not accurately detect arrhythmias because the FHR is re-sampled to a uniform sampling rate and sophisticated signal-processing methods (such as a variation of autocorrelation or cross-correlation) are used. Moreover, FHR is not reliably measured or displayed if it is over 210 bpm or less than 50 bpm. Currently available fetal electrocardiography (ECG) monitoring systems, either invasive using scalp electrodes or noninvasive using electrodes placed on the maternal abdominal wall, are not suitable for the detection and accurate diagnosis of arrhythmias as they filter irregular heartbeats, have a low resolution, and display ECG waveforms as an average of several cardiac cycles.[1] Fetal magnetocardiography and different ultrasound modalities allow the analysis of different cardiac cycle mechanical time intervals, but currently available devices are not suitable for intrapartum continuous fetal heart monitoring.

During uterine contractions, uteroplacental perfusion is reduced. In addition, umbilical cord compression during the contraction alters fetal cardiac loading conditions, and if umbilical cord compressions occur frequently, they can lead to fetal metabolic acidosis. In fetal sheep, repeated intermittent umbilical cord occlusions (UCOs) mimicking umbilical cord compression in labor activate the parasympathetic nervous system that causes fetal bradycardia observed as variable FHR decelerations on CTG registration that are followed by prolonged and more prominent FHR decelerations if the myocardial hypoxia further deepens.[2–4] In human fetuses, conduction abnormalities have been described in labor[5,6] and can contribute to bradycardia, suggesting that sinus bradycardia due to increased parasympathetic activity may not be the sole cause of FHR deceleration.

Therefore, we developed a fetal sheep model, in which we induced severe fetal metabolic acidosis by intermittent UCOs at term gestation. We hypothesized that intermittent UCOs leading to worsening fetal metabolic acidosis provoke distinct fetal arrhythmias that could indicate impending fetal death.

Key message

Continuous electrocardiographic monitoring of fetal sheep heart during intermittent umbilical cord occlusions gradually leading to severe metabolic acidemia revealed several fetal arrhythmias including atrioventricular block, ventricular tachycardia, and ventricular fibrillation that would have gone unnoticed with current fetal monitoring systems.

2 | MATERIAL AND METHODS

A total of 13 animals of Aland landrace sheep with time-dated singleton or twin pregnancies (Lammastila Sikka Talu, University of Turku, Rymättylä, Finland) were included in this study. Sheep were transported to the Oulu Laboratory Animal Centre at the University of Oulu, Finland, and allowed to adapt for a minimum of 2 weeks before the experimentation. Sheep were monitored several times daily by a veterinarian, animal technicians, and investigators for signs of pain, distress, injury, or disease. The focus was to ensure the well-being of the animals and to minimize pain.

2.1 | Fetal instrumentation

Sheep fetuses were instrumented at 133–135 days of gestation (term 145 days), which corresponds to approximately 37 weeks of human gestation. Pregnant sheep were premedicated with intramuscular ketamine (Ketaminol vet; Intervet, Boxmeer, The Netherlands) 2 mg/kg and midazolam (Midazolam Hameln; Hameln Pharmaceuticals, Hameln, Germany) 0.2 mg/kg. The maternal jugular vein was cannulated to obtain intravenous (i.v.) access, and an infusion of lactated Ringer's solution was given at a rate of 200 mL/h. The mother was given a single dose of prophylactic antibiotic, cefuroxime 1.5 g i.v. (Cefuroxime Orion, Orion Pharma Oyj, Espoo, Finland). General anesthesia was induced with i.v. propofol (Profast, Baxter Holding B.V, Utrecht, Netherlands) 4–7 mg/kg, and the ewe was intubated. The

anesthesia was maintained with a 2%–2.5% sevoflurane (AbbVie S.r.l., Campoverde di Aprilia, Italy) in an oxygen-air mixture and propofol-infusion at a rate of 0.5–1 mL/h (Profast, Baxter Holding B.V, Utrecht, Netherlands). The maternal auricular artery was cannulated with a 22F cannula for invasive blood pressure monitoring. Analgesia was provided with 50 μg fentanyl i.v. (Fentanyl Hameln, Hameln pharma gmbh, Hameln, Germany) prior to and every 1 h during the surgery or earlier, based on maternal blood pressure and heart rate changes during surgical stimuli.

Sheep was placed supine with a left lateral tilt. A lower midline incision was performed to access the uterus and the fetus through a hysterotomy, and the fetal upper body was exteriorized. In the case of a twin pregnancy, only one fetus was instrumented. Nonocclusive polyvinyl catheters were inserted into the axillary artery and jugular vein, with the catheter tips in the ascending aorta and superior vena cava pointing towards the heart. ECG electrodes were made using a shielded 3-conductor cable (AS633-3SSF, Cooner Wire, Chatsworth, CA, USA), and they were placed subcutaneously on the fetal chest.[7] A 12-mm vascular occluder (In Vivo Metrics, Healdsburg, CA) was placed around the umbilical cord at its abdominal insertion site, and the occluder was fixed to the abdominal wall with a suture to avoid it kinking the umbilical cord. In addition, EEG electrodes were connected to the fetus for another study. A separate polyvinyl catheter was placed in the amniotic cavity to measure amniotic fluid pressure. Injection of penicillin G (1 million units; Geepenil; Orion Oyj, Espoo, Finland) was administered to the fetus. Lost amniotic fluid was replaced with warm sterile 0.9% saline. The uterus was closed with a purse string suture. After the closure of the laparotomy incision, the catheters and cables were tunneled subcutaneously and exteriorized through a small incision in the ewe's flank. Postoperative analgesia was provided with 100 mg bupivacaine (Bupivacaine Accord 5 mg/mL; Accord Healthcare B.V., Utrecht, The Netherlands) injected locally into the surgical wounds and with transdermal fentanyl patches (Fentanyl-ratiopharm; Ratiopharm, Ulm, Germany), at the dose rate of 2 μg/kg/h, applied to the ewe's antebrachium before surgery. The ePatch Holter device (Philips, Koninklijke Philips N.V., Netherlands) with a sampling rate of 250 Hz was connected to the ECG electrodes to continuously record fetal ECG. The Holter device's resolution was 16 bits with 0.05 Hz high pass frequency response filter according to the manufacturer's description.

2.2 | Experimental protocol

The experiment was performed after a 4- to 5-day recovery period (Figure 1). The fetal arterial and venous catheters were connected to the BIOPAC data acquisition system (MP150, BIOPAC Systems, Inc., USA) for continuous blood pressure recording. Fetal blood pressures were referenced to intra-amniotic pressure. Fetal ECG was also connected to the BIOPAC data acquisition system to allow for online monitoring and continuous ECG recording at a 1000 Hz sampling rate while simultaneously recording with the Holter device. To detect the exact timing of the occlusion and the amount of pressure applied to the umbilical cord occluder, it was connected to a pressure monitor and the BIOPAC system.

Following a 30-min baseline ECG recording, the umbilical cord occluder was inflated with sterile water for 1 min, maintaining the occluder pressure at 600 mmHg to ensure complete umbilical cord occlusion without the risk of occlusion failure, and then deflated for 2 min, mimicking the active second stage of labor in humans with 3–4 contractions per 10 min.[8] This intermittent umbilical cord occlusion was repeated until a significant metabolic acidemia that was predefined as fetal arterial blood pH <7.00 and/or base excess (BE) less than −16 mmol/L was reached.[9,10] Fetal arterial blood samples for blood gas analyses (Abbot i-STAT 1, i-STAT, East Windsor, NJ, USA) were taken at baseline and after every 5th occlusion or earlier if needed. When a significant fetal metabolic acidosis was diagnosed, the sheep was anesthetized as described above. The fetus was delivered by emergency cesarean section while continuously recording fetal ECG and other invasive parameters. The neonate was intubated with a cuffed intubation tube while the umbilical cord was still intact. Blood samples were taken immediately from the umbilical vessels. Delayed umbilical cord clamping was applied. After the correct location of the intubation tube was confirmed by detecting exhaled CO_2 and rise of the chest, ventilation was continued with room air (FiO_2 21%). Cardiopulmonary resuscitation (CPR) (3:1) was started after 30 s of ventilation if the heart rate remained less than 60 bpm, and FiO_2 was set to 100%. If CPR with FiO_2 of 100% did not result in HR increase above 60/min, a 50 μg bolus of adrenaline (Adrenalin 0.1 mg/mL, Takeda Austria GmbH, Austria) was administered intravenously with a flush of saline every 3 min. The newborn weight

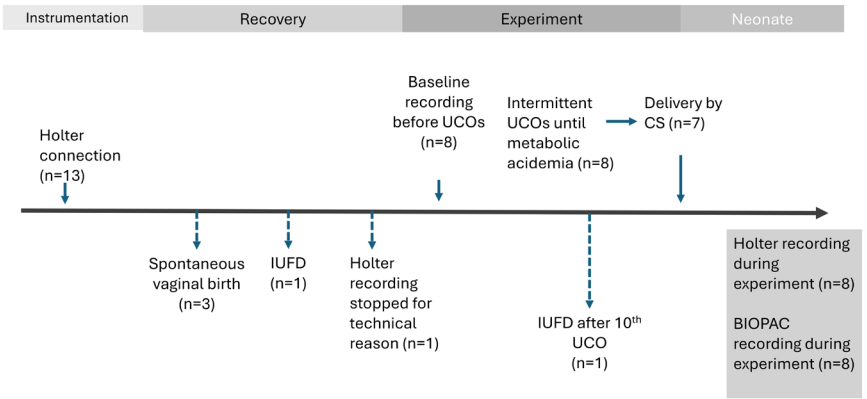

FIGURE 1 Flow chart describing the timeline of the study. CS, cesarean section; IUFD, intrauterine fetal death; UCOs, umbilical cord occlusions.

and gender were determined after birth. The newborn sheep were connected to a ventilator (Maquet Servo-i, Getinge, Gothenburg, Sweden), sedated with continuous alfaxalone infusion 1.5–9 mg/kg/h and boluses (1 mg/kg), and received continuous glucose infusion. As a part of another study, they were cared for up to 48 h by experienced neonatologists (PK and KR) in a fully equipped incubator and continuously monitored (SpO_2, heart rate, invasive blood pressure, $etCO_2$, minute ventilation, and temperature). At the end of the follow-up period, the newborn sheep were euthanized with an overdose (100 mg/kg) of pentobarbital (Mebunat vet; Orion Oyj, Espoo, Finland). The ewes were euthanized at the end of the cesarean section with an overdose (100 mg/kg) of pentobarbital (Mebunat vet; Orion Oyj, Espoo, Finland).

2.3 | Data analyses

Holter recorded ECG data were downloaded for offline analysis using the Cardiologs (Philips, Koninklijke Philips N.V.) software. The BIOPAC data were stored and analyzed offline with the AcqKnowledge (BIOPAC Systems, Inc., USA) software.

Cardiologs software is a cloud-based software powered by artificial intelligence (AI) to streamline ECG analysis. Its AI-based algorithms detect different types of events and process the data to provide suggestions for diagnoses. However, the algorithms of the Cardiologs software are designed for human adult use and did not diagnose the recorded fetal cardiac rhythm automatically. Therefore, the Holter recording was visually checked for arrhythmias and compared with simultaneously recorded BIOPAC data by two investigators (JL and JJ) to confirm the ECG segments with abnormal rhythms, which were later analyzed in detail together with a Maternal-Fetal Medicine specialist (GA) and a Pediatric and Perinatal cardiologist (SES) with a special interest in the diagnosis of fetal and neonatal arrhythmias. Fetal and neonatal arrhythmias (Figure 2) were classified according to the nomenclature recommendations of AHA/ACCF/HRS Scientific Statement.[11] Normal PR interval in fetal sheep during normoxia has been reported to be approximately 75 ms.[12]

The PR, P-P, and R-R intervals were measured (milliseconds, ms) with the measurement tool of the Cardiologs software for specific cardiac cycles when arrhythmias were detected. The amplitude of the ECG recording was optimized to have all the ECG characteristics visualized, and illustrative ECG recordings were captured and stored as figures.

2.4 | Statistics

Mean and standard deviation (SD) were calculated for the blood gas values and acid–base status. Two groups were defined according to whether the fetuses met the predefined criteria for significant metabolic acidosis following the 5th UCO (i.e., within 15 min) (Group A) or required 10 or more UCOs (Group B).

3 | RESULTS

Of a total of 13 sheep fetuses that were instrumented, one fetus died in utero and three sheep went into spontaneous labor before reaching the experimental day. In the fifth fetus, data were not continuously recorded by the Holter device due to connection problems.

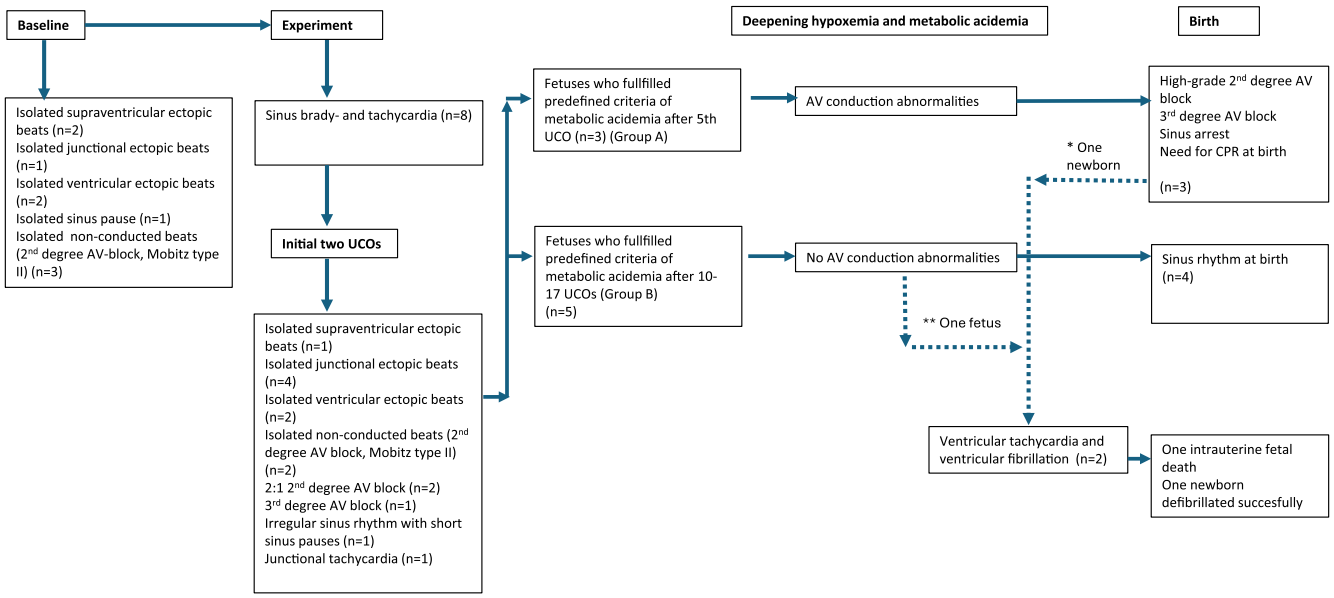

FIGURE 2 ECG findings and outcomes of the experiment. *One newborn with 3rd AV block and no detectable QRS complexes at birth developed ventricular tachycardia and fibrillation during CPR and was defibrillated. **One fetus developed ventricular tachycardia and fibrillation after 10th UCO. AV, atrioventricular; CPR, cardiopulmonary resuscitation; IUFD, intrauterine fetal death; UCOs, umbilical cord occlusions.

Review of Holter recordings during the recovery period in these five fetuses did not show any life-threatening arrhythmias. Eight sheep fetuses were successfully experimented on, and all of these were included in the final analysis (Figure 1). The mean (SD) birthweight was 2.94 (0.18) kg.

At baseline, all eight fetuses had normal arterial blood gas and lactate values (Table 1). Figure 2 summarizes the fetal ECG findings and outcomes of the experiment.

During the 30 min baseline fetal ECG recording, isolated ectopic beats were found in five fetuses: supraventricular in two, junctional in one, and ventricular in two. Short sinoatrial (SA) node pauses were recorded in one fetus, and isolated non-conducted P-waves with constant PR intervals in preceding beats (Mobitz type II second-degree atrioventricular (AV) block) were found in three fetuses.

UCOs resulted in sinus bradycardia (FHR deceleration), followed by sinus tachycardia (FHR acceleration) after the occluder was released in all fetuses except for three that had AV conduction abnormalities and severe metabolic acidemia after five UCOs.

During the first two UCOs, two fetuses had isolated supraventricular ectopic beats, four fetuses had isolated junctional ectopic beats, and two fetuses had isolated ventricular ectopic beats (Figure 2). Two fetuses had Mobitz type II and 2:1 second-degree AV block, and a third fetus had third-degree AV block with irregular junctional escape beats followed by sinus bradycardia with few ectopic junctional beats (Figure 3A,B). These three fetuses did not have any AV-conduction abnormalities later during the experiment. Another fetus had irregular sinus rhythm with short pauses and junctional ectopic beats during the first two UCOs (Figure 3C). After the first UCO was released, regular junctional ectopic tachycardia occurred (Figure 3D). Following the release of the second UCO, the rhythm was initially sinus tachycardia followed by a short period of either ventricular or junctional ectopic tachycardia with aberration (Figure 3E).

After five UCOs, three out of eight fetuses (two male and one female, mean birthweight 2986 g, SD 48 g) developed severe metabolic acidosis requiring prompt delivery by cesarean section (Group A, Table 1). They all showed a similar pattern of persistent AV-conduction abnormalities during and after the release of the last UCO (Figures 2 and 4). Initially, sinus bradycardia with a normal PR interval and occasional sinus pauses and arrest was noted (Figure 4A). Thereafter, prolonged AV conduction with PR intervals of 130–170 ms together with Mobitz type II and 2:1 to 8:1 severe second-degree AV block (Figure 4B,C), and finally complete third-degree AV block and prolonged sinus arrest. After the last UCO was released and fetal oxygenation started, sinus activity (P-waves) recovered first followed by ventricular activity (QRS complexes). Finally, a regular sinus rhythm was restored. All these fetuses required CPR and subsequent i.v. adrenaline after birth (Figure 2). One of these fetuses that had third-degree AV block developed polymorphic ventricular tachycardia (VT) followed by a more uniform VT soon after birth during CPR after a long period without mechanical ventricular function (Figure 5C). Following CPR, irregular sinus node activity was restored without any AV conduction or escape rhythm in the ventricles (Figure 5C). It was followed by a gradual increase in the number of ventricular ectopic beats (Figure 5D). Approximately 2 min after the spontaneous cessation of the uniform VT, ventricular fibrillation (VF) was triggered at a rate close to 600 bpm (Figure 5D,E). Successful defibrillation (4 J/kg) was performed, converting to sinus rhythm (Figure 5F).

Five fetuses (three male, one female and sex information missing for one fetus; mean birth weight 2907 g, SD 231 g) required 10 or more UCOs before they developed severe metabolic acidosis indicating emergency cesarean section (Group B, Table 1). None of these fetuses showed any AV-conduction abnormalities during severe metabolic acidosis (Figure 2). However, an increase in the frequency of supraventricular or ventricular ectopic beats was

TABLE 1 Fetal arterial blood gases, pH, lactate, and base excess values in the ascending aorta at baseline, after fifth umbilical cord occlusion and before delivering the fetus with emergency cesarean section, and in the umbilical artery at birth. Group A = Fetuses who fulfilled the predefined criteria of metabolic acidemia after five UCOs. Group B = Fetuses who fulfilled the predefined criteria of metabolic acidemia after 10–17 UCOs.

	pH	pO_2 (kPa)	pCO_2 (kPa)	BE (mmol/L)	Lact (mmol/L)
Baseline (Group A, $n=3$)	7.37 (0.04)	2.50 (0.24)	5.48 (0.55)	−1 (4)	2.08 (0.40)
Baseline (Group B, $n=5$)	7.38 (0.03)	2.15 (0.34)	5.85 (0.64)	1 (4)	2.62 (1.73)
After 5th UCO[a] (Group A, $n=3$)	6.86 (0.12)	1.70 (0.70)	14.88 (1.69)	−14 (6)	9.59 (2.49)
After 5th UCO (Group B, $n=5$)	7.26 (0.07)	1.67 (0.34)	6.98 (0.93)	−3 (6)	4.60 (1.31)
Before CS (Group B, $n=4$)[b]	6.98 (0.02)	2.15 (0.27)	7.93 (1.20)	−17 (1)	9.50 (1.57)
At birth (Group A, $n=3$)	6.84 (0.17)	2.93 (0.93)	13.33 (2.49)	−17 (6)	11.44 (1.66)
At birth (Group B, $n=4$)[b]	6.90 (0.04)	2.60 (0.62)	11.79 (1.54)	−16 (1)	14.54 (1.59)

Note: Mean values (SD, standard deviation). pH, pO_2, and pCO_2 temperature correlated with 39°C.

Abbreviations: BE, base excess; CS, cesarean section; kPa, kilopascal; Lact, lactate, mmol/L, millimoles per liter; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; UCO, umbilical cord occlusion.

[a]Blood gas values taken after 5th UCO in group A were taken just prior to cesarean section.

[b]One fetus died in utero after 10th UCO.

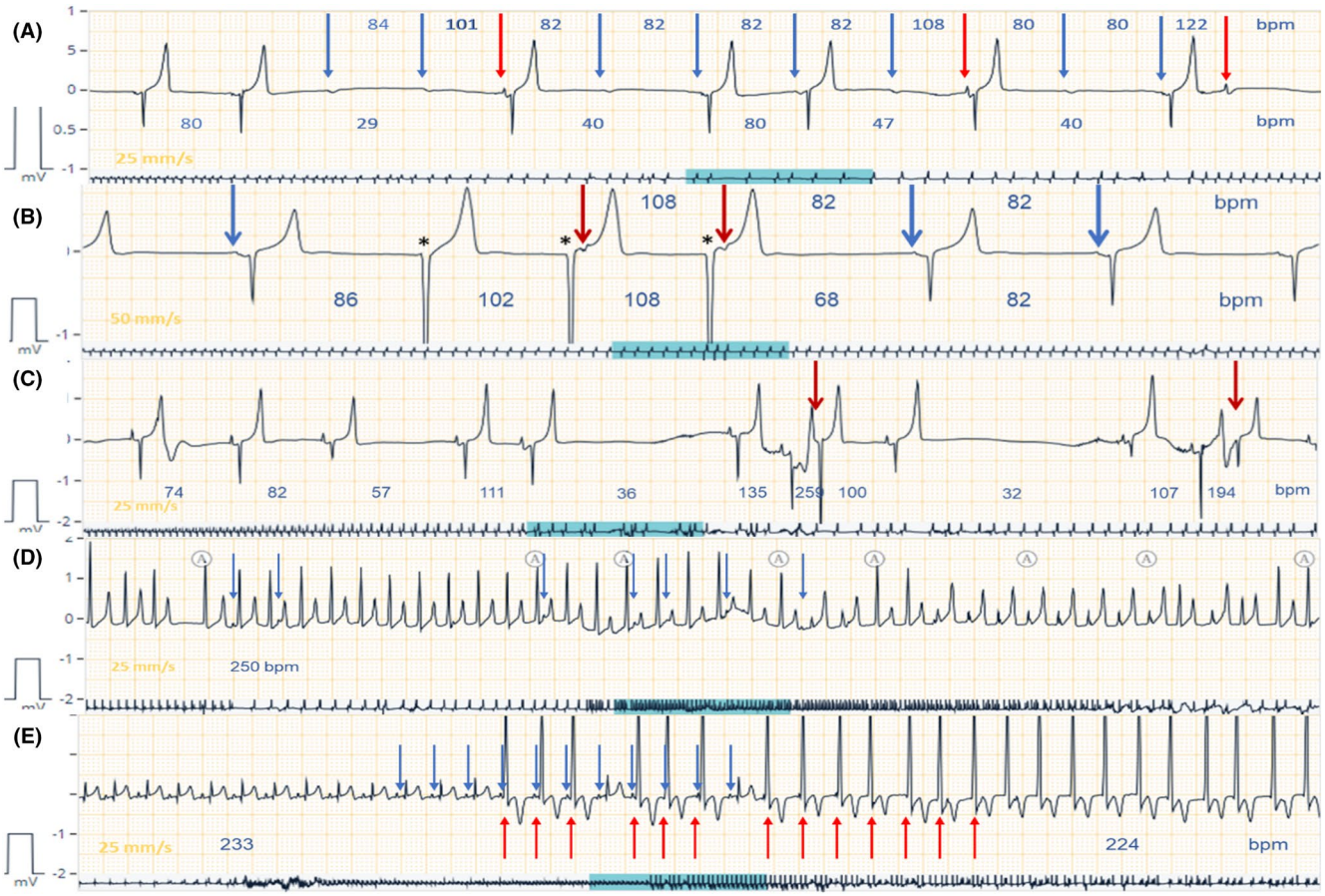

FIGURE 3 ECG findings during the first two umbilical cord occlusions. In this and subsequent figures, the upper trace of each panel shows the blue shaded part of the lower trace on an extended time scale. (A) During the 1st umbilical cord occlusion (UCO), sinus bradycardia of 80–85 bpm (blue arrows) with few ectopic atrial depolarizations (red arrows). Most likely complete atrioventricular dissociation (3rd degree AV block) with irregular junctional escape beats (QRS complexes are narrow suggesting that they are generated in the lower node-His region of the AV node). (B) During the 1st UCO, sinus bradycardia (82 bpm, blue arrows) with a series of three ectopic slightly premature junctional beats (*). Two of the beats are followed by P'-waves (red arrows) as a result of retrograde conduction to the atria and reset of the sinus node; the P'P-interval is the same as the following PP interval (82 bpm). (C) During the 1st UCO, slow irregular sinus rhythm with short pauses of 1.7–1.9 s and a few isolated premature junctional ectopic beats (red arrows). (D) After the 1st UCO was released, regular junctional ectopic tachycardia with a rate of approximately 250 bpm occurred. QRS complexes are narrow and dissociated from a slower atrial rhythm, hidden in the QRS complexes (blue arrows), suggesting a focus below the atria in the lower node-His region of the AV node. (E) After the release of the 2nd UCO, sinus tachycardia (233 bpm) followed by ventricular or junctional ectopic tachycardia with aberration (red arrows) and a slightly lower rate. Note the premature start of the ectopic arrhythmia without retrograde conduction and the effect on the atrial rhythm that remain stable (blue arrows).

observed during and immediately after the release of UCO that was followed by sinus tachycardia (Figure 6). One of these fetuses in a sinus rhythm accompanied by premature ventricular extrasystoles developed polymorphic VT (approximately 660 bpm) with a progressive change in the amplitude and polarity of the QRS complexes leading to VF and intrauterine death before delivery after the 10th UCO (Figure 7C).

4 | DISCUSSION

Umbilical cord occlusion, when performed intermittently and repeatedly, leads inevitably to severe fetal metabolic acidosis. During UCO and immediately after its release, fetal cardiac loading conditions are changing abruptly and drastically. This study tested the hypothesis that intermittent UCOs leading to worsening fetal metabolic acidosis provoke distinct fetal arrhythmias that could indicate impending fetal death. A wide variety of different fetal arrhythmias during or after the release of UCO was observed, including supraventricular and ventricular ectopic beats that are considered to be benign with no fetal adverse outcome. However, some fetuses developed life-threatening arrhythmias, that is, AV-conduction abnormalities without escape rhythm in the ventricle or VT/VF, during worsening metabolic acidosis.

When the umbilical cord is completely occluded, an increase in parasympathetic activity triggers a decrease in FHR, and an increase in sympathetic activity promotes peripheral vasoconstriction and centralization of blood flow to critical organs. After the occlusion

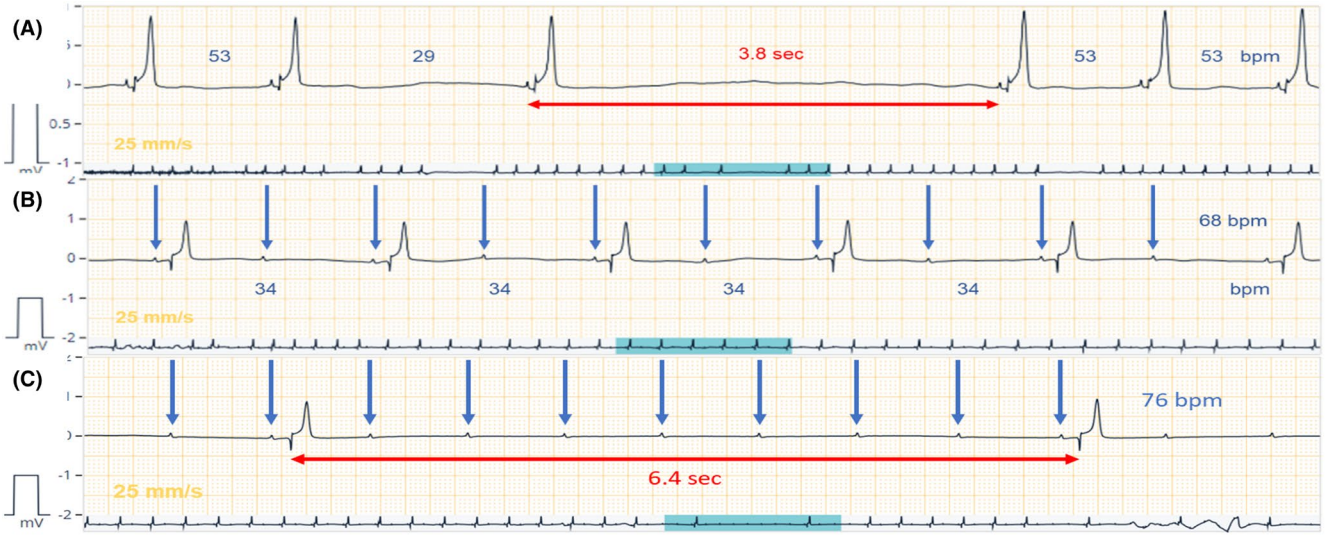

FIGURE 4 Persistent atrioventricular conduction abnormalities during metabolic acidemia. (A) ECG tracing during the last umbilical cord occlusion (UCO) before predefined criteria for cesarean section were fulfilled, showing severe sinus bradycardia (53 bpm, decreasing to 29 bpm) with normal atrioventricular (AV) conduction (59 ms) and an arrest of sinus node activity for 3.8 s (red arrow) during severe metabolic acidemia. (B) After the last UCO was released and preparing for emergency cesarean section. Sinus bradycardia (68 bpm, blue arrows) with 2:1 2nd degree AV block. Conducted beats with a PR interval of 130 ms. (C) Preparing for emergency cesarean section after the last UCO. Sinus bradycardia (76 bpm, blue arrows) with 2:1 and a period of 6.4 s (red arrow) with high-grade 8:1 2nd degree AV block. Conducted beats with a PR interval of 170 ms.

is released, compensatory tachycardia develops. These physiologic changes in FHR reflect normally functioning peripheral chemoreflex.[4,13,14] Some fetuses demonstrated transient AV-conduction abnormalities during the initial UCOs that were not present anymore later during the experiment. Most likely, these AV-conduction problems were related to an excess vagal response that affects SA and AV nodes. These findings are in agreement with a previous fetal sheep study.[15] Furthermore, atropine administration has been shown to prevent UCO-related AV-conduction abnormalities, supporting the concept that increased parasympathetic activity affects the fetal cardiac conduction system.[16] Immediately after the release of UCO, ectopic beats, and transient junctional VT preceded sinus tachycardia, compensating for the FHR decrease when the SA node was still under vagal stimulus before it fully recovered. Junctional tachycardia and extra beats during variable deceleration are associated with good fetal outcome.[17] After these transient arrhythmia episodes, sinus tachycardia was restored showing activation of peripheral chemoreflex and adrenergic response[14,18,19] counterbalancing the vagal effects on FHR.

Three fetuses tolerated only five UCOs before developing severe metabolic acidosis. At baseline conditions, blood gas values were within the normal physiologic range. All of them had AV-conduction abnormalities with a poor escape rhythm in the ventricles and required CPR after delivery. Potential factors limiting cardiac adaptation to altered loading conditions include a restrictive foramen ovale,[20] insufficient myocardial glycogen reserves,[21] or loss of junctional escape rhythm leading to severe bradycardia and asystole.[17] Worsening fetal metabolic acidemia first affected the AV node, leading to a progressive impairment of conduction, from incomplete to complete AV block. At the same time, the automaticity in the lower AV-node-His region decreased to the extent that complete AV block was followed by ventricular asystole. SA node activity persisted as P-waves were seen even after the AV conduction and ventricular activation ceased. Finally, the SA node activity became irregular, demonstrating longer pauses leading to prolonged sinus arrest. Recovery began with the restoration of SA node activation, followed by gradual AV-node activation. The action potential in SA and AV nodes has been shown to decrease during hypoxia, and the SA-node recovery is prolonged only during severe anoxia.[22] Prolonged PR interval likely reflected conduction delay in the AV-node and His-Purkinje fibers due to subendocardial myocardial damage caused by hypoxia rather than vagal stimuli, as seen in mid-gestation human fetuses[23] as well as near-term sheep fetuses.[24] Our findings support the concept that AV node is more sensitive to hypoxemia and metabolic acidemia than the SA node.

Other sheep fetuses tolerated significantly more UCOs before they met the criteria for the cesarean section. None of these fetuses showed any abnormalities in AV conduction during worsening metabolic acidosis. However, supraventricular or ventricular ectopic beats were commonly observed during and immediately after the release of UCOs. In one fetus, ventricular ectopic beats during worsening metabolic acidemia triggered a sudden VT/VF that led to fetal demise. Furthermore, one newborn with only irregular sinus node activity present at birth developed VT/VF during CPR. Successful defibrillation restored sinus rhythm. VT/VF could explain a sudden intrapartum intrauterine fetal demise in cases without prior preterminal changes or prolonged bradycardia on CTG. Abnormalities in the myocardial conduction system that could provoke electrical dyshomogeneity, instability, and desynchronicity leading to malignant arrhythmias under specific conditions have been identified in

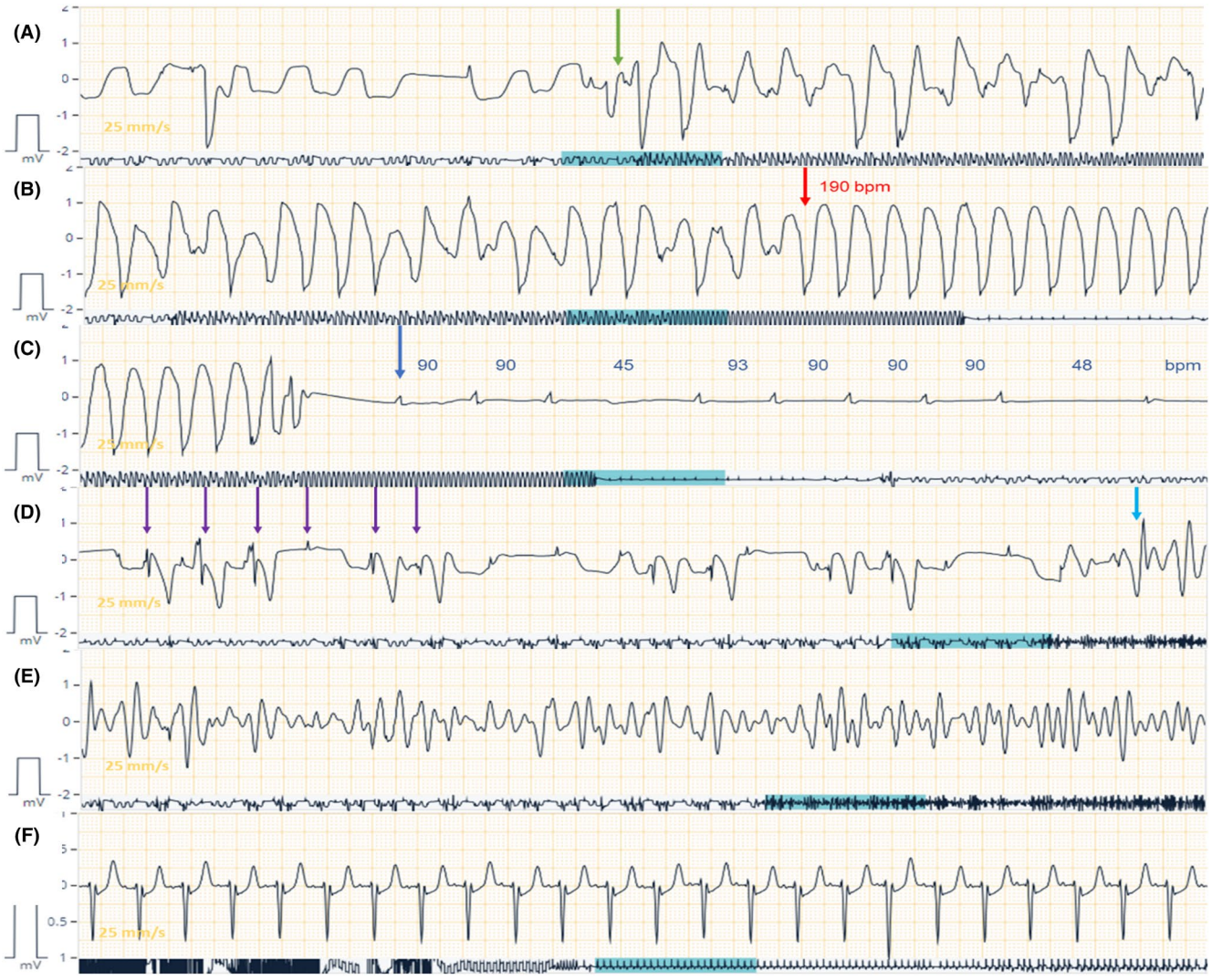

FIGURE 5 (A–F) Recordings during postnatal resuscitation (3:1 cardiopulmonary resuscitation) of a sheep born without mechanical ventricular function. The first cardiac electrical activity noted was a polymorphous ventricular rhythm (A) that within 30 s developed to a more uniform ventricular tachycardia (190 bpm) lasting for slightly less than 20 s (B, C) and, in turn, followed by a slightly irregular sinus node activity (90 bpm) without any atrioventricular conduction or escape rhythm in the ventricles (C). During the following minutes, there were no signs of improvement in atrioventricular conduction, but a gradual increase of ventricular ectopic beats (D) that approximately 2 min after the spontaneous stop of the uniform ventricular tachycardia turned into ventricular fibrillation with a rate of close to 600 bpm (D, E). After defibrillation, sinus rhythm at a rate of 134 bpm, PR interval 100 ms (F). (Green arrow = start of polymorphous ventricular rhythm; red arrow = start of uniform ventricular tachycardia; blue arrow = start of irregular sinus node activity; purple = ventricular ectopic beats; light blue arrow = start of ventricular fibrillation).

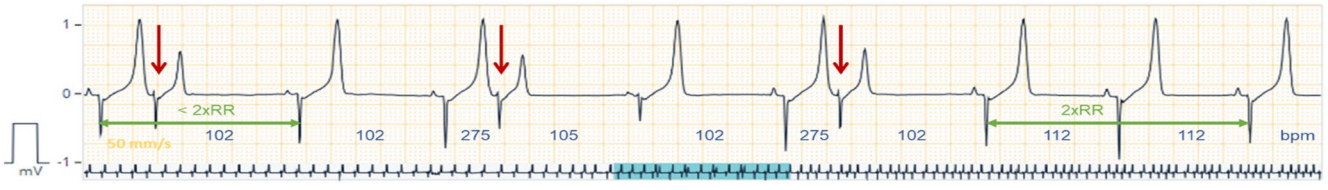

FIGURE 6 During umbilical cord occlusion, sinus bradycardia (appr. 110 bpm) with isolated premature supraventricular ectopic beats (red arrows). The ectopic beats reset the sinus node and result in an incomplete compensatory (<2 × RR interval).

fetuses with intrauterine demise.[25] Hypoxia, metabolic acidemia, and increased catecholamine levels can trigger VF in children.[26]

In human fetuses, few studies have analyzed the cardiac rhythm with ECG during labor. Mohajer et al.[6] analyzed the raw scalp ECG, without using group averaging techniques, and documented sinus bradycardia and complete AV block when FHR fell below 60 bpm. Supraventricular and ventricular ectopic beats, AV block, and sinus pauses and arrests have been detected during FHR deceleration.[27,28]

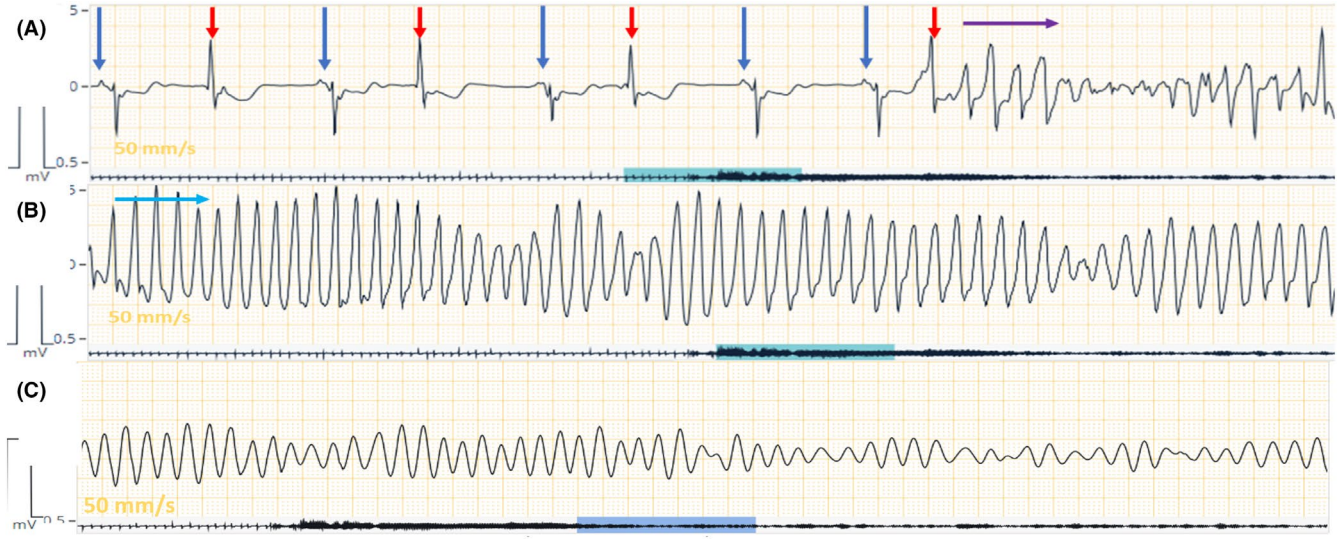

FIGURE 7 (A–C) After the 10th umbilical cord occlusion was released, (A) sinus rhythm 122 bpm (blue arrows), with three premature ventricular extrasystoles in bigeminy (red arrows), followed by two sinus beats and a final premature ventricular beat (red arrow) starting a polymorphic ventricular tachycardia (violet arrow) with progressive change in the amplitude and polarity of the QRS complexes (light blue arrow) and a rate of approximately 660 bpm (B) and finally to ventricular fibrillation (C).

One strength of our present study is that the gradually worsening metabolic acidemia following intermittent UCOs in near-term non-anesthetized sheep mimics the complicated human labor when oxygen delivery is compromised during uterine contractions. In previous fetal sheep studies, UCOs were performed in earlier gestations, with different UCO-reperfusion intervals or under general anesthesia. Another strength of our study is that we acquired fetal ECG by two different modalities. The comparison between Holter ECG with a sampling rate of 250 Hz to simultaneously obtained raw unfiltered ECG signals recorded at a much higher sampling rate (1000 Hz) confirmed that the Holter device recorded high-quality fetal ECG signals that were adequate for arrhythmia detection.

Some previous sheep studies performing intermittent UCOs have shown that the fetuses tolerate many more UCOs compared with ours before meeting the criteria of significant metabolic acidemia.[2,29] However, in those studies, the occlusion (1 to 2 min) and reperfusion times have varied (1.5 to 4 min). Moreover, those studies were done in earlier gestations, and premature sheep fetuses have been shown to tolerate hypoxemia better.[30]

The sex[31] and weight of the fetus might also influence their ability to respond to UCOs. In our small sample of cases, we did not find any substantial differences in the response to hypoxia attributed to sex or body weight, and it remains unclear why three of our fetuses did not tolerate the intermittent UCOs as long as the others.

This study has also some limitations. The Holter monitoring device is designed for adult use, limiting automatic diagnosis and quantification of fetal arrhythmias. Furthermore, ECG was recorded from three electrodes placed under the fetal skin. It may not be possible to obtain a similar quality ECG from human fetuses, even using the high-quality scalp electrodes.

New devices and signal-processing methods are being developed to acquire good-quality fetal ECG. Recent efforts have centered on improving signal quality, minimizing noise from maternal ECG and external interference, and developing wearable or patch-based systems that are comfortable for prolonged use. Several such systems are in various stages of regulatory clearance, commercial availability, clinical testing, and validation. Most manufacturers use noninvasive, patch-based fetal ECG monitors for real-time maternal and FHR monitoring, such as Meridian M110 (MindChild Medical, Inc., USA), Monica Novii Wireless Patch System (GE, Healthcare, USA), Nemo Fetal Monitoring System (Nemo Healthcare, the Netherlands), and INVU system (Nuvo Group, USA). Technical details are not always transparently revealed, but most of them still average multiple beats or have limited sampling frequencies, potentially missing beat-to-beat irregularities crucial for arrhythmia diagnosis.[32–35] Although they report accurate FHR monitoring, none have been rigorously tested specifically for detecting and characterizing fetal arrhythmias. There is accordingly a need to develop new or improve existing fetal monitoring devices to be able to detect fetal arrhythmias during labor.

5 | CONCLUSION

Worsening fetal sheep metabolic acidemia induced by intermittent UCOs is associated with various arrhythmias including supraventricular or ventricular ectopic beats that are usually thought to have no adverse effect on fetal outcome. However, some fetuses developed life-threatening arrhythmias, that is, AV-conduction abnormalities or VT/VF during metabolic acidosis. AV-conduction abnormalities may occur during FHR decelerations that probably do not look exactly like variable decelerations but still mostly go unnoticed with current fetal monitoring techniques. This study demonstrates the feasibility of long-term fetal ECG recording at a sufficient resolution (sampling rate of ≥250 Hz) for detecting arrhythmias using a Holter device.

Fetal ECG monitoring by improved scalp electrodes coupled with a software capable of automatically detecting significant arrhythmias could enhance intrapartum fetal monitoring in the future.

AUTHOR CONTRIBUTIONS

Designing the study: JJ, GA. Experimental animal work and data acquisition: JL, JJ, HH, MH, KR, PK, H-MV, JV, JR, GA. Data analysis and processing: JL, JJ Interpreting data: JL, JJ, S-ES, GA. Drafting manuscript, figures and tables: JL. Reviewing the manuscript critically and revising the manuscript: all authors. Final approval of revised manuscript: all authors.

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ETHICS STATEMENT

The study protocol was approved by the National Animal Experiment Board of Finland (ESAVI/8401/2021) on April 12, 2021. The animal care and experiments were performed in compliance with the national legislation,[36] EU directive,[37] and the ARRIVE 2.0 guidelines.[38]

ORCID

Juulia Lantto https://orcid.org/0000-0002-5136-1434
Sven-Erik Sonesson https://orcid.org/0000-0002-7004-504X
Ganesh Acharya https://orcid.org/0000-0002-1997-3107

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