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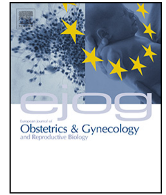

Full length article

The change of fetal heart rate short-term variability during the course of histological chorioamnionitis in fetal sheep

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ABSTRACT

Objective: Histological chorioamnionitis (CAM) is related to neonatal mortality and morbidity. However, identifying intrauterine inflammation before delivery is challenging. The aim of this study was to investigate the changes in fetal heart rate (FHR) short-term variability (STV) during the course of histological CAM.

Study Design: Changes in STV were measured in 7 chronically instrumented fetal sheep at 111–120 days of gestation. Lipopolysaccharide (LPS) was infused into the amniotic cavity for 2 days following the 4th postoperative day to develop histological CAM. STV was determined based on the R to R interval of the fetal electrocardiogram. We continued to observe the changes in STV until the time of intrauterine fetal death (IUFD). The umbilical cord and fetal membranes were evaluated histologically after IUFD. The experiment was divided into two phases: 1) the acute phase, defined as the 24-hour period between the first and second injections of LPS and 2) the perimortem phase, defined as the period between the second injection of LPS and IUFD. Changes in STV in both the acute and perimortem phases were evaluated using Friedman's test. A probability of <0.05 was accepted as statistically significant.

Results: The fetuses died, on average, at 23.7 ± 4.9 h after the second injection of LPS. Both the umbilical cord and fetal membranes showed histological evidence of severe inflammation. During the perimortem phase, there were statistically significant differences in STV at each time point. STV increased significantly at 6, 4, and 3 h before intrauterine fetal death compared to the baseline.

Conclusion: Our study suggests that STV increased as the fetal condition deteriorated during the course of histological CAM.

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Introduction

Chorioamnionitis (CAM) is a common obstetrical complication that is associated with poor maternal outcomes (specifically postpartum infection and sepsis) and adverse fetal or infant outcomes, such as neonatal sepsis, and neurodevelopmental disabilities [1–3]. Histological CAM that is confirmed by histological examination after birth is one form of CAM. Histological CAM is also related to severe fetal outcomes, not only those mentioned above, but may sometimes result in intrauterine fetal death (IUFD) [4]. Presently, the method of diagnosing histological intrauterine inflammation in the antenatal period is nonspecific.

Since 1960, fetal heart rate (FHR) monitoring has been commonly used worldwide for assessing fetal well-being during the antepartum and intrapartum periods [5]. Traditionally, baseline FHR variability is a key indicator of fetal condition because the presence of FHR variability indicates appropriate fetal oxygenation [6]. Furthermore, FHR monitoring assessments during the course of intrauterine inflammation are especially important because the fetus is thought to be vulnerable to hypoxic-ischemic stress when exposed to inflammatory mediators [7].

There are few studies that have identified associations between histological CAM and FHR patterns [8–10], and the results are conflicting. Such studies have potential limitations, including the lack of longitudinal observation of FHR variability using objective evaluation methods [8].

In animal experiments, with regard to the correlation between endotoxemia and FHR variability, Lear et al. reported that endotoxemia induced by lipopolysaccharide (LPS) was related to transient increases in FHR variability, and that repeated exposures to LPS led to the progressive loss of FHR variability [11], but histological examination was not conducted. Currently, the longitudinal changes in FHR variability that occur during the course of histological CAM are not well known. Therefore,

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we observed the longitudinal changes in quantitative FHR variability, specifically short-term variability (STV) in histological CAM induced by LPS in chronically instrumented preterm fetal sheep. Quantification of STV was performed using the R to R interval on the fetal electrocardiogram [12]. Histological CAM was induced by infusion of LPS into the amniotic cavity.

Materials and methods

Animal preparation

This study was approved by the Animal Ethics Committee of the Fukushima Medical University (No 26036). Seven pregnant Corriedale/Suffolk sheep (Japan-lamb Co., Ltd, Fukuyama city, Japan) were surgically instrumented between 113 and 120 days of gestation (term = 145 days). General anesthesia was induced by intramuscular injection of xylazine (Bayer Yakuhin Ltd, Osaka, Japan) (0.2 mg/kg), followed by intravenous injection of dexmedetomidine hydrochloride (Maruishi Pharmaceutical Co., Ltd, Osaka, Japan) (3 mg/kg/min) [13]. Using aseptic technique, a midline skin incision was made. The fetal head was delivered thorough a hysterotomy incision and covered with a surgical globe filled with warm saline.

Polyvinyl catheters (1.8 mm outer diameter and 1.2 mm inner diameter., Imamura Co. Ltd., Tokyo, Japan) were placed into the fetal carotid arteries, fetal jugular veins, amniotic cavities, and maternal femoral veins. The fetal blood samples were collected from the carotid arteries, and the fetal jugular veins were used for injection of the drug agents. Antibiotics were administered via the maternal femoral veins. Electrodes attached to polyvinyl-coated stainless-steel wires (Tesco Co., Ltd, Tokyo) were placed on the fetal trunks and the bilateral upper limbs to record the fetal electrocardiograms. All fetal catheters, electrodes, and maternal catheters were exteriorized through the maternal flank.

As part of the post-operative care, the ewes were housed in metabolic cages with free access to food and water, and were exposed to 12-hour cycles of dark/light (light 6:00–18:00 h). The room temperature was controlled at 18 ± 2 °C. After surgery, antibiotics were administered through the maternal vein (1 g flomoxef sodium. Biological half life: 49.2 min. Shionogi Co., Ltd, Tokyo) every 12 h for 3 days, until the first injection of LPS.

Experimental protocol (Fig. 1)

Each experiment was performed 48 h after surgery. We partially referred to a study of Watanabe et al. [14] to formulate the histological CAM model. A total of 50 μg of granulocyte-colony stimulating factor (G-CSF: Neutrogin R. Chugai Co. Ltd, Tokyo) solubilized in 2 ml of saline was injected intravenously into the fetuses on postoperative days 3–6. Forty milligrams of LPS (Escherichia coli 055:B5 endotoxin; Sigma Aldrich Co. LLC, St. Louis, Missouri, USA) solubilized in 10 ml of saline was administered by bolus infusion into the amniotic cavity on postoperative days 5 and 6. We continued to observe the FHR and STV until IUFD (Fig. 1).

Fetal arterial blood collection (Fig. 1)

We divided the experiment into 2 phases (acute and perimortem phases). The acute phase was defined as the 24-hour period between the first and second injections of LPS. The perimortem phase was defined as the time period from the second LPS injection until IUFD.

Fetal arterial blood samples were collected at three points. The first sampling point was the control, taken just before the first injection of LPS. The second sample, for the 24-hour data, was taken 24 h after the first injection of LPS. The third sample, for the perimortem data, was collected during the perimortem phase.

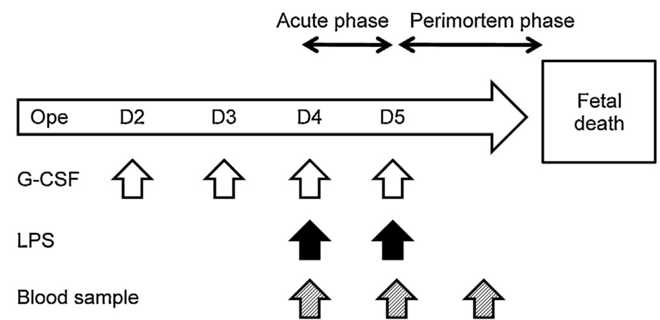

Fig. 1. Experimental protocol. Granulocyte-colony stimulating factor (G-CSF) was injected intravenously into the fetuses. Lipopolysaccharide (LPS) was injected into the amniotic cavity. The experiment was divided into two phases (acute and perimortem). Fetal arterial blood samples were collected at three points. 1) The control sample was taken just before the first injection of LPS. 2) The 24-hour sample was taken 24 h after the first injection of LPS. 3) The perimortem sample was collected during the perimortem phase. Ope: operation, LPS: lipopolysaccharide.

Fetal arterial blood gas was analyzed at each of the three points using a blood gas analyzer (Corning 170 pH/Blood gas Analyzer system) with the temperature corrected to 38 °C.

Measurement of FHR

The FHR was measured using the acquisition system (Power Lab, AD Instruments, Australia). For the FHR calculations, the individual R-waves from the fetal electrocardiograms, with sample rates of 1 kHz, were sequentially recognized. The distance between the consecutive R wave peaks was measured, and then converted to beats per minute. At least 20 min of mean stable baseline FHR recording was converted to an hourly value.

Quantification of variability

Variability measures were quantified by loading electrocardiographic signals directly acquired from the FHR using the Power Lab system into the ATM1308 Variability Calculate System (Atom Medical, Tokyo), an on-line animal experimental data display/recording device. The resting rate (R-R) interval of the acquired FHR signals were converted into beats per minute. Then, the difference in rate between the two contiguous intervals was calculated. STV was denoted when the sign of interval FHR was different for two contiguous intervals [15]. STV values were accumulated for 100 consecutive R-R intervals and reset [12]. STV was measured 10 points during a stable 20-min FHR segment at each point converted to an hourly value.

Histological examination and scoring of inflammation

After fetal death, the fetuses were weighed. The umbilical cord and rolls of chorion and decidua were placed into 10% buffered formalin for fixation. We classified the severity of inflammation of the umbilical cord and fetal membranes into one of six scoring categories. This classification scheme is based on the established methods and scoring system by Salafia and Navaro [16,17] (Table 1). The scoring of inflammation was evaluated by a single pathologist who was blinded to the study design.

Statistical analysis

In each experiment, the baseline value of the physiological parameters was defined by the 1 h preceding the first LPS

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