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Alteration of FHR pattern and cerebral metabolic rate of glucose of the fetus measured by positron emission tomography during progress of acidemia. The significance of overshoot acceleration in FHR

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1 Introduction

It is well known that striking changes in brain function occur in utero hypoxic-ischemic insult. Such changes lead not only to impairment of brain function but also to lifethreatening damage to the fetus and neonate. In order to quickly assess possible deteriorating fetal condition from hypoxic-ischemic insult, fetal heart rate (FHR) monitoring has been widely accepted as accurate and reliable in the clinical setting. However, there have been no reports of studies examining periodical change in fetal brain function while recording FHR when the fetus is suffering from hypoxic-ischemia. It would be quite valuable for us to be able to correctly evaluate according to alterations in FHR pattern, the extent to which fetal brain function will be impaired, and whether the fetal brain will incur permanent damage unless immediate intervention is undertaken. Since glucose, as well as oxygen, is a principal substrate for meeting the energy demand of the brain, measurement of the rate at which this substrate is utilized provides an assessment of the level of neuronal function in the brain. In this report positron emission tomography (PET), which involves tracer kinetic measurement of a compound labeled with a positron emitting isotope and is recently used in experimental perinatal medicine [4], was utilized in a noninvasive approach to assess the fetal cerebral glucose metabolic rate (CMRglc) in hypoxic ischemia while recording FHR which showed a characteristic overshoot acceleration.

Curriculum vitae

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2 Materials and methods

Animal preparation: Four chronically instrumented lamb fetuses of around 130 days gestation (term, approximately 150 days) were studied. Under general anesthesia, the uterus was exposed through a midline abdominal incision. Through a small incision in the uterus, polyvinyl catheters (ID, 1.36 mm; OD, 2.08 mm) were aseptically inserted into a femoral artery and vein of the fetus, Tripolar cardioelectrodes were applied to the chest of the fetus, positioned on each side of the heart, and the third one on the back of the fetus. An inflatable cuff (OC-16, In Vivo Metric Inc.) was placed around the umbilical cord to induce mechanical cord compression. After completing the closure of the uterine wall, another small incision was made in the uterus.

The fetal head was pulled up and fixed at the maternal abdominal wall by several stitches with silk thread. With this procedure the location of fetal head was easily identified in the PET study.

Induction of acidemia in the fetus: Gradually-progressive acidemia was induced in the fetus by intermittently repeated cord compression achieved by inflating the cuff placed around the cord. Serial compression was performed in such a fashion that a combination of compression lasting for 40 seconds followed by release for 80 seconds was repeated 15 times and, thereafter, a combination of 60 seconds of compression and release for 60 seconds was repeated 30 times. The total duration of the cord compression study was 90 minutes. Fetal arterial blood was sampled every ten minutes following the release of cord compression. Blood gas was analyzed using the AVL-300 system (AVL, U. S. A.).

FHR monitoring: Tripolar cardioelectordes were applied in the fashion described above. FHR was monitored with a cardiotachometer triggered by the cardioelectric signal.

Positron emission tomography (PET): On the forth or fifth postoperative days, utilization of glucose in the fetal brain before and after the onset of acidemia was investigated using PET, while observing the alteration of FHR pattern. Since anesthesia of the maternal ewe may affect the metabolism in the fetus, respiration of the maternal ewe was maintained by ventilation with room air, following intubation and administration of pancuronium to prevent body movement. The maternal ewe was laid on its side on the movable table of the PET instrument and a transmission scan was made. The radionucleotides were produced at the Cyclotron and Radioisotope Center, Tohoku University. F^{18}-2-fluoro-2-deoxyglucose (F^{18}-FDG) was produced by bombardment of Ne^{20} gas with deuterium oxide. The position of the fetal brain, which was fixed to the maternal abdominal wall with several stitches of silk thread, was ascertained by X-ray photographs taken prior to the PET. Following the transmission scan. 1.0 mCi of F^{18}-FDG in one ml of saline was administered to the fetus through a tube placed in the fetal vein. The uptake of F^{18}-FDG in fetus through the tube placed in the fetal vein. The uptake of F^{18}-FDG in the fetal brain was scanned with an ECAT-II (ORTEC, U. S. A.), which is equipped with a ring of detectors giving images with a slice thickness of 15 mm and a resolution of 13 mm. After completion of the scan, cord compression was carried out according to the procedure described above. When compression had proceeded to the point where arterial pH was around 7.15, and a characteristic overshoot acceleration appeared in FHR, 5.0 mCi of F^{18}-FDG was administered to the fetus again and the scan performed in the same manner. Fetal arterial blood samples of 0.2 – 0.5 ml were taken before and during the PET study for blood gas analysis as well as measurement of radioactivity and blood sugar concentration. Image reconstruction was done by computer. Quantification of FDG uptake was attempted using mean pixel counts in the region of the fetal brain. Absolute values of CMRglc were obtained according to the equation originally developed by Sokoloff et al [6].

3 Results

Gradually progressive fetal acidemia was induced by serial cord compression. Although the details of FHR change in progress of acidemia have been previously reported [2], typical patterns observed in the experiment are shown in figure 1. The condition of the maternal ewe remained good during the PET study as evaluated by periodic blood gas analysis while respiration was maintained in the fashion described above. The change in FHR pattern with the progress of fetal acidemia induced by repeated cord compression was almost identical to that previously reported [5], even when the maternal ewe was ventilated in this fashion. Namely, a characteristic FHR pattern including overshoot acceleration immediately after release of cord compression appeared when fetal arterial pH had fallen below 7.15. The repeated cord compression brought about fetal metabolic acidosis in which fetal arterial pH fell, concentration of lactate increased and PCO_2 exceeded 100 mmHg, although PO_2 dropped transiently during each cord comprssion [5]. CMRglc of the fetal brain was studied in nonacidemic and acidemic conditions, in which FHR showed a characteristic overshoot acceleration. Fetal arterial values during these periods are listed in table I. After completion of cord compression, the fetal arterial pH remained low in two cases and had slightly recovered in the other two cases, at the point of CMRglc measurement. In all cases, blood glucose level in the fetus rose when the fetus became

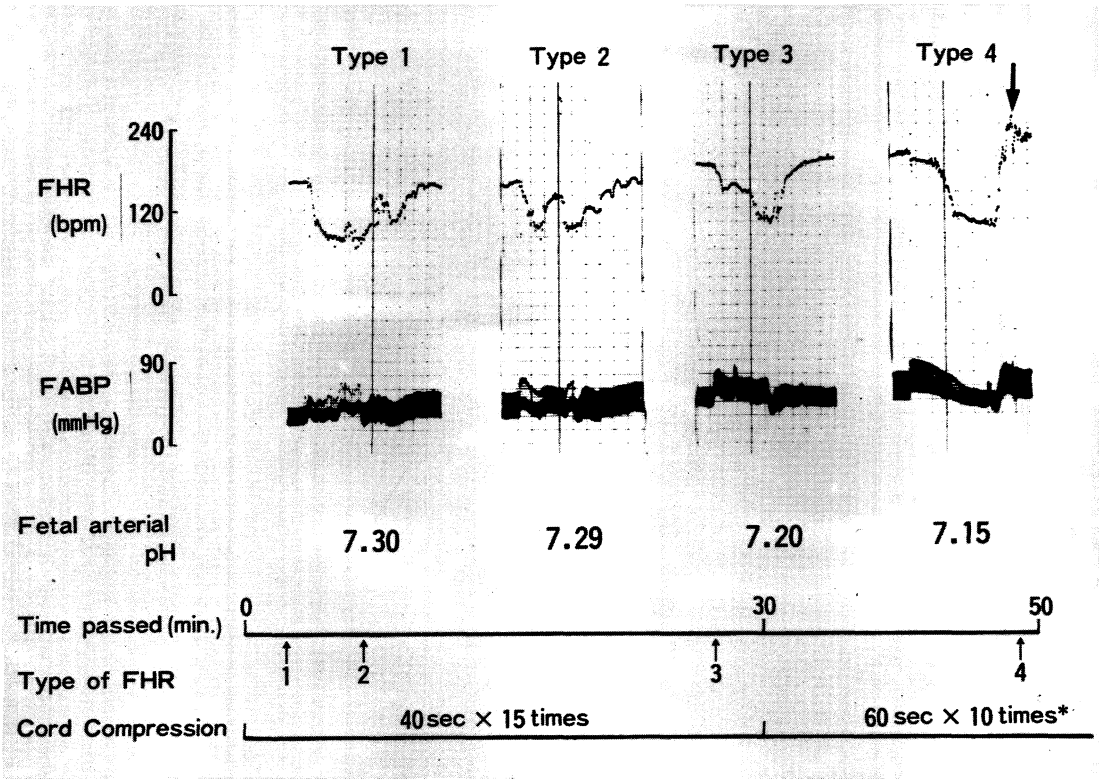

Figure 1. Typical FHR patterns in repeated cord compression. Type 4 in which fetal arterial pH falls to around 7.15 includes a characteristic overshoot acceleration which appears immediately after release of cord compression. The arrow shows an overshoot acceleration immediately after the release of cord compression.

Table I. Fetal arterial pH before and after repeated cord compression and at the appearance of overshoot acceleration in FHR. Blood glucose level in the fetus before and after cord compression "After cord compression" refers to the time of measurement of CMRglc by PET. CC: cord compression

	Gestation Age (day)	Fetal arterial pH			Blood glucose (mg/dl)	
		before CC	overshoot	after CC	before CC	after CC
No. 1	120	7.314	7.150	7.106	18.5	37.1
No. 2	121	7.310	7.135	7.250	6.8	12.2
No. 3	125	7.350	7.157	7.294	24.2	26.2
No. 4	119	7.334	6.950	6.970	30.5	32.2
Mean	121.3	7.327	7.098	7.155		

acidemic due to cord compression (table I). Images of F^{18}-FDG accumulation in the fetal brain and records of FHR and fetal arterial blood pressure (FABP) in nonacidosis and acidosis are shown in figures 2 and 3, respectively. Comparing the two images, utilization of glucose in the fetal brain is obviously decreased in the acidemic condition. As shown in table II, CMRglc in the fetal brain in the nonacidemic condition was 1.73 $\pm$ 0.59 mg/100 g/min (M $\pm$ S.D.) as a mean of four experiments. On the other hand, the CMRglc in the acidemic condition cased by the cord compression was significantly lower, 0.73 $\pm$ 0.55 mg/100 g/min, compared to that in the normal condition. The mean decrease in CMRglc was 55%.

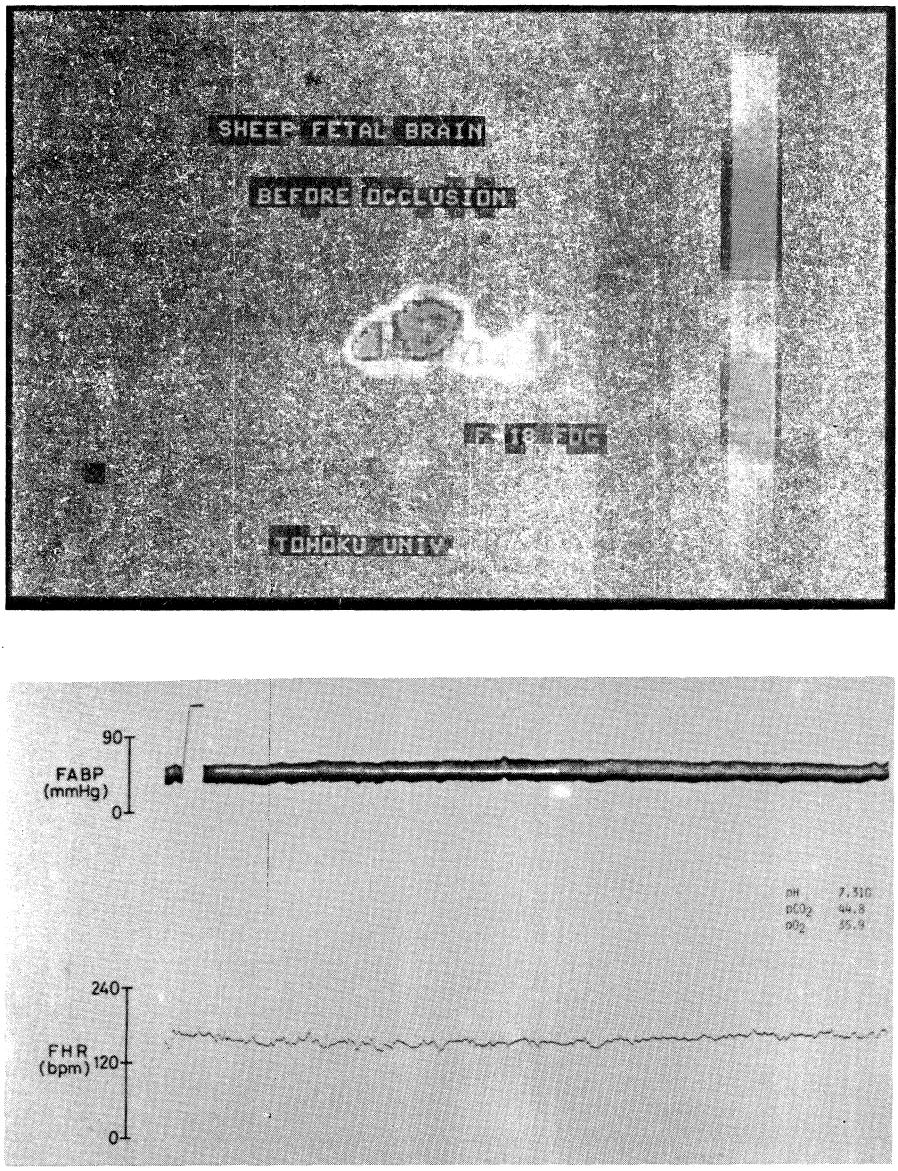

Figure 2. Image of accumulation of F^{18}-FDG in fetal brain and FHR and fetal arterial blood pressure (FABP) records before the repated cord compression. Fetal arterial pH was 7.310 and other blood gas values show good fetal condition. Variability in FHR is normal.

4 Discussion

The main purpose of this study is to determine the point in FHR where the fetus was distressed enough sustain irreversible damage to principle organs including the brain. In this study we focused on the significance of overshoot acceleration in FHR. The significance of overshoot acceleration in FHR was first proposed by Goodlin et al [3]. According to their explanation, the occurrence may reflect immaturity of fetal heart rate control. In the present and previous paper [5] we suggest that overshoot acceleration

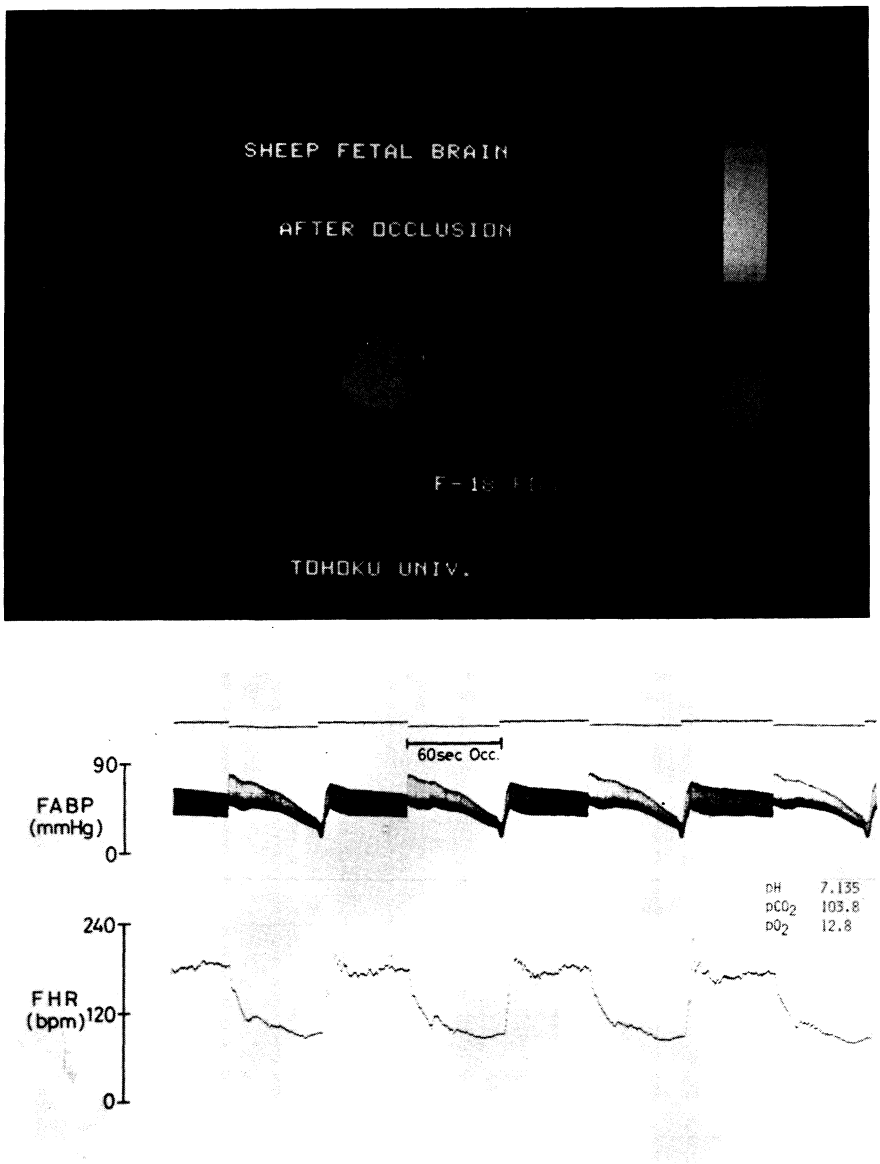

Figure 3. Image of accumulation of F^{18}-FDG in fetal brain and FHR and FABP records after repeated cord compression. Fetal arterial pH was 7.135 and pCO_2 increased in this case. FHR shows a characteristic pattern, type 4, with an overshoot acceleration. Occ: cord compression.

may appear when the fetus has become so acidotic that brain metabolism is severely disturbed. Specifically in the present study, we measured CMRglc in the fetus while recording FHR and re-evaluated the importance of overshoot acceleration for a better understanding of the FHR pattern. In a previus paper [2, 5], we also demonstrated that at appearance of overshoot acceleration, arterial pH decrease below 7.15 and catecholamines such as noradrenaline and adrenaline are released and reach a plateau at over 10 ng/ml in arterial blood. Increase blood glu-

Table II. Cerebral glucose metabolic rate in sheep fetus before and after the repeated cord compression

Exp.	CMRglc before cord compression (mg/100 g/min)	CMRglc after cord compression (mg/100g/min)	reduction rate (%)
No. 1	1.41	0.21	85
No. 2	2.61	1.32	49
No. 3	1.46	1.16	21
No. 4	1.44	0.41	71
Mean ± S.D.	1.73 ± 0.59*	0.78 ± 0.55*	55

*$p < 0.05$

cose level in the acidotic fetus may be due to the release of catecholamines. The release of catecholamines probably leads to completion of the redistribution of blood flow for the sake of vital organs. Actually, carotid artery flow increases while that of the femoral artery decreases in the acidemic fetus at the appearance of overshoot acceleration when the blood flow of those vessels are concurrently measured by transit time ultrasonic blood flow meters surgically installed around the vessels (data not shown). Although the blood flow of the carotid artery does not necessarily reflect cerebral blood flow, we think that decrease in CMRglc in such acidotic fetus may not derive from the decrease of cerebral blood flow but from inactivity of cellular function of the fetal brain.

When we look at changes in CMRglc in four experiments, reduction rate was high in two cases in which fetal arterial pH was constantly low during the period from the appearance of overshoot in FHR to CMRglc measurement of PET, whereas in the other two cases the reduction rate was not so. Since we ceased cord compression at the appearance of overshoot acceleration in FHR, recovery of the fetal condition, which should be responsible for the reduction of CMRglc rate might depend on placental function in the respective cases. If we encounter overshoot acceleration in FHR, intervention becomes necessary to prevent devastation of the fetus. Otherwise the duration of the acidemia may disturb brain function, eventually leading to cell death, bringing about irreversible neuronal sequelae.

Abstract

In order to investigate the significance of overshoot acceleration in FHR with acidosis induced by serial cord compression, cerebral glucose metabolic rate (CMRglc) was measured in four chronically instrumented fetuses before cord compression and immediately after appearance of the overshoot acceleration in FHR. The investigation of CMRglc was carried out using positron emission tomography to assess accumulation of cyclotron-produced F^{18}-FDG in the fetal brain. CMRglc in the fetal brain in the nonacidemic condition was 1.73 mg/100 g/min. In acidemia, with fetal arterial pH near 7.15 in which FHR showed the characteristic pattern with overshoot acceleration, CMRglc was significantly decreased to 0.73 mg/100 g/min. We concluded that, to avoid neuronal damage, it is necessary to intervene when the fetal condition deteriorates to the extent that overshoot acceleration in FHR occurs.

Keywords: Cerebral metabolic rate of glucose, fetal acidemia, fetal heart rate, positron emission tomography.

Zusammenfassung

Messung von Herzfrequenzveränderungen und Veränderungen im zerebralen Glukosemetabolismus mit der Positronemissionstomographie während einer Azidose. Bedeutung einer überschießenden FHR-Akzeleration

Wir untersuchten die Bedeutung überschießender FHR-Akzelerationen bei Azidosen, die durch mehrere Nabelschnurkompressionen induziert wurden. Dazu bestimmten wir die Rate des zerebralen Glukosemetabolismus (CMRglc) bei vier apparativ dauerüberwachten Feten vor der Nabelschnurkompression und unmittelbar nach Auftreten der überschießenden FHR-Akzeleration. Die Untersuchung der CMRglc wurde mit Hilfe der Positronemissionstomographie (PET) durchgeführt, wobei die Akkumulation von im

Zyklotron produzierten F^{18}-FDG im fetalen Gehirn gemessen wurde. Im nichtazidotischen Zustand betrug die CMRglc im fetalen Gehirn 1,73 mg/100 g/min. Bei Azidosen mit einem arteriellen pH um 7,15 zeigt die FHR die charakteristische überschießende Akzeleration und die CMRglc fällt auf 0,73 mg/100 g/min. Um Hirnschäden zu vermeiden, ist eine Intervention an dem Punkt notwendig, wenn sich der fetale Zustand in dem Maße verschlechtert, daß eine überschießende FHR-Akzeleration auftritt.

Schlüsselwörter: Fetale Azidose, fetale Herzfrequenz, Glukosestoffwechselrate im Gehirn, Positronemissionstomographie.

Résumé

Altération des tracés du RCF et taux métabolique cérébral de glucose chez le fœtus mesuré par tomographie à émission de positrons au cours de l'évolution de l'acidose. Signification des accélérations aïgues du RCF
Afin d'explorer la signification des accélérations aïgues du RCF lors d'acidoses induites par des compressions du cordon en série, on a mesuré le taux métabolique cérébral de glucose (CMRglc) chez quatre fœtus chroniquement cathétérisés avant compression du cordon et immédiatement après l'apparition d'accélérations aïgues du RCF. L'étude du CMRlgc a été réalisée à l'aide de tomographies à émission de positrons qui apprécient l'accumulation de F18 – FDG produits par cyclotron dans le cerveau fœtal. En l'absence d'acidose, le CMRglc dans le cerveau fœtal est de 1.73 mg/100 g/min. Lors d'acidose, avec un pH artériel fœtal voisin de 7.15, au cours de laquelle le RCF montre des aspects caractéristiques avec des accélérations aïgues, le CMRlgc chute de façon significative à 0.73 mg/100 g/min. Nous en concluons donc que, afin d'éviter des lésions neuronales il est nécessaire d'intervenir lorsque l'état fœtal se détériore jusqu'à l'apparition d'accélérations aïgues sur le RCF.

Mots-clés: Acidose fœtale, rythme cardiaque fœtal, taux métabolique cérébral de glucose, tomographie à émission de positrons.

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