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INTRAPARTUM HYPOXIA AND POWER SPECTRAL ANALYSIS OF FETAL HEART RATE VARIABILITY

by

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The great tragedy of Science

– the slaying of a beautiful hypothesis by an ugly fact.

Thomas H. Huxley

English biologist (1825 - 1895)

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Intrapartum hypoxia and power spectral analysis of fetal heart rate variability

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ABSTRACT

Reliable detection of intrapartum fetal acidosis is crucial for preventing morbidity. Hypoxia-related changes of fetal heart rate variability (FHRV) are controlled by the autonomic nervous system. Subtle changes in FHRV that cannot be identified by inspection can be detected and quantified by power spectral analysis. Sympathetic activity relates to low-frequency FHRV and parasympathetic activity to both low- and high-frequency FHRV.

The aim was to study whether intra partum fetal acidosis can be detected by analyzing spectral powers of FHRV, and whether spectral powers associate with hypoxia-induced changes in the fetal electrocardiogram and with the pH of fetal blood samples taken intrapartum. The FHRV of 817 R-R interval recordings, collected as a part of European multicenter studies, were analyzed. Acidosis was defined as cord pH $\leq$ 7.05 or scalp pH $\leq$ 7.20, and metabolic acidosis as cord pH $\leq$ 7.05 and base deficit $\geq$ 12 mmol/l.

Intrapartum hypoxia increased the spectral powers of FHRV. As fetal acidosis deepened, FHRV decreased: fetuses with significant birth acidosis had, after an initial increase, a drop in spectral powers near delivery, suggesting a breakdown of fetal compensation. Furthermore, a change in excess of 30% of the low-to-high frequency ratio of FHRV was associated with fetal metabolic acidosis.

The results suggest that a decrease in the spectral powers of FHRV signals concern for fetal wellbeing. A single measure alone cannot be used to reveal fetal hypoxia since the spectral powers vary widely intra-individually. With technical developments, continuous assessment of intra-individual changes in spectral powers of FHRV might aid in the detection of fetal compromise due to hypoxia.

Key words: fetal heart rate variability, power spectral analysis, hypoxia, metabolic acidosis

Saila Siira

Sikiön synnytyksenaikainen hapenpuute ja sikiön sykevaihtelun tehospektianalyysi

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TIIVISTELMÄ

Sikiön synnytyksenaikaisen hapenpuutteen luotettava tunnistaminen on tärkeää, jotta voidaan estää vastasyntyneen sairastavuutta. Synnytyksenaikainen hapenpuute aiheuttaa autonomisen hermoston välityksellä muutoksia sekä sikiön syketasoon että sykevaihteluun. Näitä sikiön sykevaihtelun, osin silmälle näkymättömiä muutoksia voidaan tutkia tehospektrianalyysin avulla. Sympaattinen aktivaatio näkyy sykevaihtelun spektrin matalataajuuskaistoissa ja parasympaattinen aktivaatio sekä matala- että korkeataajuuskaistoissa.

Tutkimuksien tavoitteena oli selvittää miten 817 sikiön sykevaihtelun spektrikaistat muuttuvat synnytyksen aikana, miten eri spektrikaistat korreloivat synnytyksen aikana sikiön päänahasta mitattuun pH arvoon, ja miten sykevaihtelun muutokset heijastuvat syntymän jälkeiseen happo-emästaseeseen. Tutkimuksessa selvitettiin myös, miten sykevaihtelun spektrikaistojen muutos sikiö-EKG:n ST-hälytyksen yhteydessä korreloi sikiön metaboliseen asidoosiin (syntymä-pH $\leq$ 7,05 ja emäsvaje (BD) $\geq$ 12 mmol/l).

Sykevaihtelun spektrianalyysi osoitti selkeitä eroja hapenpuutteisen ja terveen sikiön välisessä synnytyksenaikaisessa sykevaihtelussa. Lievässä hapenpuutteessa spektritehot ensin nousevat, mutta hapenpuutteen vaikeutuessa ja asidoosin ilmaantuessa sykevaihtelun spektritehot laskevat. Tutkimus osoitti myös, että synnytyksen kuluessa sykevaihtelu muuttuu selvästi sikiö-EKG:n ST-muutosten yhteydessä niillä sikiöillä, jotka eivät pysty mukautumaan hapenpuutteeseen synnytyksen aikana vaan joille kehittyy perinataalivaiheessa metabolinen asidoosi.

Tulokset viittaavat siihen, että sikiön sykevaihtelun spektritehojen pieneneminen synnytyksen aikana varoittaa sikiön kompensaatiokyvyn heikkenemisestä. Koska yksilöllinen spektrikaistojen vaihtelu on suurta, ei yksittäisellä mittauksella voida identifioida hapenpuutteista sikiötä, mutta sikiön sykevaihtelun spektritehojen muutosten seuraaminen synnytyksen kuluessa voisi auttaa hapenpuutteisen sikiön tunnistamisessa.

Avainsanat: sikiön hapenpuute, sikiön sykevaihtelu, tehospektrianalyysi

CONTENTS

ABBREVIATIONS

ANS	autonomic nervous system
apH	umbilical artery pH
BD	base deficit
BP	blood pressure
bpm	heartbeats per minute
c/b	cycles per beat
CTG	cardiotocography
ECG	electrocardiogram
FBS	fetal scalp blood sampling
FFT	Fast Fourier transform
FHR	fetal heart rate
FHRV	fetal heart rate variability
GA	gestational age
h	hour
HF	high-frequency
LF	low-frequency
LF/HF	low-to-high frequency ratio
MF	mid-frequency
min	minute
ms	millisecond
rel	relative spectral power (power divided with total power)
ROC	receiver operating characteristic
RR	risk ratio
s	second
STAN®	automated ST- analysis
US	ultrasound
VLF	very-low-frequency

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by their roman numerals (I-IV).

I Rantonen T, Ekholm E, Siira S, Metsälä T, Leino R, Ekblad U, Välimäki I: Periodic spectral components of fetal heart rate variability reflect the changes in cord arterial base deficit values: a preliminary report. Early Human Development 2001 Jan; 60(3): 233-238. Copyright Elsevier Science Ireland Ltd.

II Siira S, Ojala T, Vahlberg T, Jalonen J, Välimäki I, Rosén KG, Ekholm E: Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. BJOG-An International Journal of Obstetrics and Gynaecology, 2005; 112: 418-423. Copyright Blackwell Publishing.

III Siira S, Ojala T, Ekholm E, Vahlberg T, Blad S, Rosén KG: Change in heart rate variability in relation to a significant ST event associates with newborn metabolic acidosis. BJOG-An International Journal of Obstetrics and Gynaecology 2007; 114: 819-823. Copyright Blackwell Publishing.

IV Siira, S, Ojala, T, Vahlberg, T, Rosén, K.G., Ekholm, E: Spectral bands of fetal heart rate variability associate with momentary fetal scalp pH. Submitted.

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1. INTRODUCTION

Oxygen supply from the mother to her fetus may be endangered during delivery. This may, in the worst case, lead to fetal cerebral damage or death. The incidence of cerebral palsy varies from 1.6 to 2.2 per 1000 *(Lie et al. 2010, Hagberg et al. 1993, Himmelmann et al. 2010, Pierrat et al. 2005)*, and intrapartum oxygen deficiency is the probable cause of 6 - 13% of these *(Himmelmann et al. 2010, Pierrat et al. 2005, Pschirrer et al. 2000, Gilbert et al. 2010)*. Intrapartum acidosis may also lead to meconium aspiration and metabolic disturbances and, later in life, to cognitive dysfunctions *(Hutter et al. 2010)*.

To prevent morbidity, early detection of fetal acidosis is crucial. The most widely used method for monitoring fetal well-being during delivery is cardiotocography (CTG), but CTG is non-specific with regard to identification of fetal acidosis. Since visual interpretation of CTG is subjective, there is a high inter- and intraobserver variability in how nonreassuring fetal heart rate (FHR) tracings are viewed by clinicians *(Chauhan et al. 2008)*. Continuous CTG monitoring may also lead to an increased numbers of cesarean sections and instrumental vaginal deliveries *(Thacker et al. 2003)*.

Fetal scalp blood sampling (FBS) is the golden standard for identification of intrapartum fetal acidosis, and is used alongside CTG. However, fetal blood sampling needs often to be repeated, and is thus time-consuming and inconvenient for the parturient. Furthermore, it is not free of complications, and fetal scalp infections and hemorrhages may ensue *(Sabir et al. 2010)*.

Recently, ST analysis of the fetal electrocardiogram (ECG) (STAN®) has been used to assess fetal wellbeing during delivery. Compared to FBS, ST analysis yields continuous information and is more convenient for the parturient. However, STAN® is also dependent on subjective interpretation of the CTG. More objective and detailed information on fetal responses to hypoxia are clearly needed.

During oxygen deficiency, the autonomic nervous system (ANS) is activated, and this causes changes in the control of FHR *(Pulgar et al. 2009)*. In an experimental animal study on a sheep, occlusion of umbilical cord caused a decrease in FHR and an increase in short-term fetal heart rate variability (FHRV) in fetuses, together with a slight decrease in pH. Increased FHRV is thought to be an important sign of adequate circulatory adaptation in the compromised fetus *(Frasch et al. 2009)*. A frequency-specific assessment of FHRV by power spectral analysis may be used to monitor features of fetal autonomic cardiac control *(Siimes et al. 1990, Sibony et al. 1994, van Ravenswaaij-Arts et al. 1993)*. Spectral analysis provides a tool for quantifying small changes in FHRV that remain undetected if heart rate tracings are only interpreted visually. In human fetuses, the value of spectral analysis for detecting changes in cardiac control is poorly known, and there have been no studies on the clinical usefulness of this technique. The aim of this thesis was to examine if spectral analysis of FHRV of term fetuses is useful in detecting intrapartum hypoxia and acidosis at birth.

2. REVIEW OF THE LITERATURE

2.1 Fetal hypoxia during delivery

2.1.1 The hypoxemic cascade

A fetus may be exposed to different degrees of oxygen deficiency during labor. Acidemia refers to a high hydrogen ion concentration in the blood. Intrapartum hypoxia may lead to acidosis, with a high hydrogen ion concentration in the fetal tissues *(Bobrow et al. 1999)*.

Intrapartum hypoxia can be divided into three phases according to how serious oxygen deficiency is. The first and mildest phase is hypoxemia, when oxygen saturation in blood is decreased, and the fetus becomes hypercapnic. At this stage, cell and organ functions remain intact. In the second phase, hypoxia, oxygen deficiency affects the peripheral tissues and acidemia develops, while central organs remain well-oxygenated. Finally, if oxygen deficiency is prolonged, the fetus switches to anaerobic metabolism for its energy. This results in metabolic acidosis of the tissues, affects the central organs and leads to organ dysfunction. This phase is called fetal asphyxia *(Peeters et al. 1979, Low 1997)*.

Intrapartum fetal acidemia can be estimated by measuring the pH or lactate from a FBS. Scalp pH-values between 7.20 and 7.25 have been considered borderline, as a scalp blood pH-value of 7.20 is the lower limit (-2 SD) of the reference range. These guidelines are the golden standard *(Bretscher et al. 1967)*. For lactate measurements, every measuring device needs its own reference values *(Nordström 2004)*. Scalp blood lactate values < 4.2 mmol/l have been considered normal, although values < 5.4 mmol/l have also been related to normal fetal outcome *(Kruger et al. 1999, Heinis et al. 2011)*.

At birth, fetal hypoxia and metabolic acidosis can be evaluated from umbilical cord blood samples. A cord artery pH-value ≤ 7.05 has been used as a marker of significant acidosis *(Amer-Wåhlin et al. 2002, Goldaber et al. 1991, Norén et al. 2003)*. However, it seems that metabolic acidosis is more closely associated with adverse fetal outcomes *(Low et al. 1994)*. Algorithms based on measured pH and Pco_2 (partial pressure of carbon dioxide) are used for calculating the umbilical artery base deficit (BD) *(Wiberg et al. 2006)*. A low pH with normal BD in a cord blood sample reflects acute respiratory acidosis, and if the BD is increased hypoxia has been more prolonged and anaerobic metabolism has ensued (Figure 1). A BD value < 8 mmol/l is considered normal, while BD values 8 - 12 mmol/l are associated with minor neonatal complications. A BD value >12 mmol/l marks for prolonged hypoxia and metabolic acidosis, which predisposes the infant to moderate or severe asphyxic complications *(Low et al. 1997, Andres et al. 1999)*.

There are no absolutely specified pH criteria or other criteria that distinguish neonates who will have injury due to intrapartum acidosis from neonates who will not. Brain damage was induced in ovine fetal brain by umbilical cord occlusion *(Ikeda et al. 1998)* and it was found that severity of brain injury correlated with the duration of hypotension, but not with the duration of bradycardia or the severity of acidosis or

hypoxia. This suggests that fetal vulnerability depends on individual reserves used to meet challenging hypoxic situations during delivery.

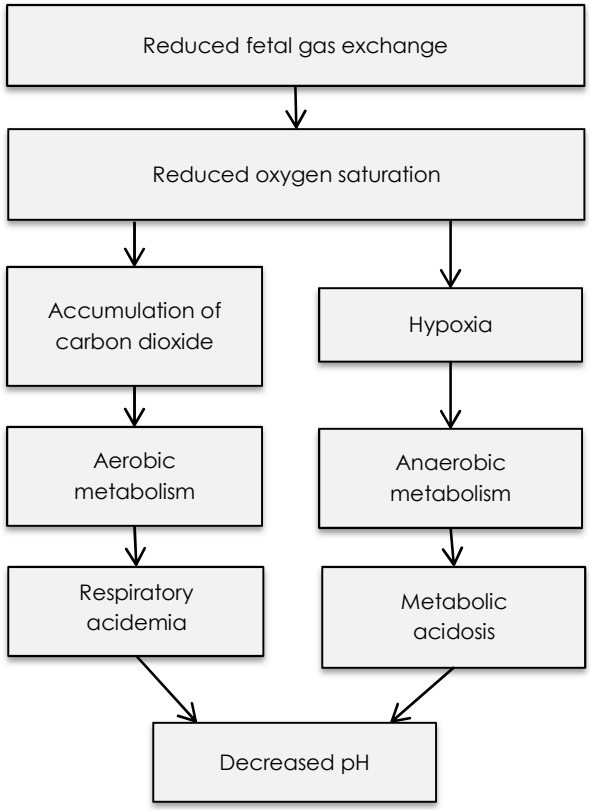

Figure 1. Development of fetal acidosis.

2.1.2 Mechanisms of fetal hypoxia

In humans, decreased perfusion through the umbilical vessels or the placenta is the most common cause for oxygen loss to the fetus *(King et al. 2000)*. Acute fetal hypoxia intra partum may occur for several reasons: compression of the umbilical cord, diminished uterine blood flow and gas-exchange, maternal hypotension or maternal oxygen deficit, abruption of the placenta, or abnormal uterine contractions. Abrupt hypoxia due to abruption of the placenta, uterine rupture or umbilical cord prolapse is a dramatic event, usually neither predictable nor preventable but usually easily detected as prolonged bradycardia in the CTG *(Westgate et al. 1999b)*. Acute maternal hypotension or oxygen deficiency is presumably also promptly noticed by caregivers, if it causes fetal hypoxia.

During the course of normal labor, there the placental gas-exchange is intermittently reduced. Hyperactive uterine contractility, often induced by oxytocin, is an important

risk factor for acidemia at birth *(Jonsson et al. 2008)*. During the contractions, the umbilical cord may be compressed in such a way that blood flow to the fetus is restricted or even stopped. This causes fetal hypertension and a rapid baroreceptor reflex. The fetal reaction to this transient oxygen deficiency is often seen as a sharp, short drop of FHR on the CTG during a contraction *(King et al. 2000)*. However, the reasons for CTG changes usually remain unclear.

The fetus may have chronic hypoxia already during (early) pregnancy due to placental insufficiency or limited maternal oxygen uptake due to some maternal disease, e.g. congenital heart disease. Chronic hypoxia may impair the ability of the fetus to cope with the stress of labor *(Hutter et al. 2010, Westgate et al. 1999b, de Haan et al. 2006)*.

2.1.3 Fetal defense mechanisms against acidosis

The development of fetal acidosis, and the perinatal outcome, depends on three factors: 1) initial status of the fetus, 2) duration of hypoxic stress intra partum, and 3) intensity of the stress *(Fleischer et al. 1982)*.

In experimental animal studies, hypoxia has been induced by reducing the inspired partial pressure of oxygen to the mother, or by reducing uterine or umbilical blood flow *(Jensen et al. 1999)*. These studies have shown that chronic hypoxia causes fetal growth retardation, increased catecholamine levels, and redistribution of blood flow to the vital organs. In these chronically hypoxic fetuses, there is no physiological increase in FHRV following maturation with advancing gestational age (GA). The FHR and blood pressure increase initially and return to baseline level with time. Constant chronic hypoxia without acidosis causes changes neither the fetal body movements nor the fetal breathing movements *(Murotsuki et al. 1997, Gardner et al. 2002, Salihagic-Kadic et al. 2006, Martin 2008, Bocking 2003)*. A simplified table of hypoxia-related changes in animal experiments is presented in Table 1.

As a consequence of chronic hypoxia, the fetus fails to achieve its genetically determined growth potential *(Hutter et al. 2010)*. Chronically compromised fetuses are not only more susceptible to peripartum hypoxia, but are also more sensitive to asphyxic damage, probably due to lower carbohydrate and other nutritional stores *(Parer 1998)*.

When a chronically hypoxic fetus is predisposed to acute hypoxia, the blood pressure rises and the redistribution of blood flow is attenuated. When the acute hypoxia is over, fetal bradycardia returns to the normal pulse rate faster than in control fetuses not chronically hypoxic. Catecholamine levels are increased and rise even further. Thus, adverse intrauterine conditions blunt the fetal responses to subsequent episodes of acute hypoxia *(Gardner et al. 2002)*. When chronically hypoxic fetuses become acidemic, FHRV gradually decreases after an initial rise. FHR is also reduced with severe acidosis *(Ikeda et al. 1998, Dalton et al. 1977)*.

Acute hypoxia induces fetal bradycardia and increases both the heart rate variability and the blood pressure of the fetus. With prolonged hypoxia, FHRV decreases, and catecholamines are released. The catecholamine levels rise in fetuses who have reduced pH-values in scalp blood samples and umbilical cord blood samples. As a

compensatory mechanism to the decreased oxygen levels, fetal blood flow is redistributed in favor of the vital organs *(Jensen et al. 1999, Gardner et al. 2002, Martin 2008, Dalton et al. 1977, Bennet et al. 2009, Thakor et al. 2009, Wassink et al. 2007)*. The compensating responses of the fetus to different degrees of oxygen deficiency are presented in Table 2.

It is speculated that acute acidemia might sensitize the fetal responses to oxygen deficiency and cause an increase in both vagal and sympathetic autonomic outflow. In an experimental animal study labor-like progressing hypoxia was induced in lamb fetuses by one-minute repeated cord occlusions. This was followed by a five-min recovery period. In this setting, FHRV did not change significantly during the four-hour study period; fetal acidosis enhanced, however, the response markedly. When the recovery period was shortened to 2.5 minutes, the fetuses developed metabolic acidosis (pH = 6.92; BD = 17 mmol/l) at the end of the study. The FHRV of these fetuses increased transiently at first, but toward the end of the study period, the FHRV decreased and there was a rapid overshoot and instability of FHR after the occlusions. Still, a couple of fetuses (which had lower lactate levels) had increased FHRV at the end of the study. Hence, the individual reactions to similarly induced hypoxia seem to differ, probably due to different initial compensating reserves *(Thakor et al. 2009, Westgate et al. 1999a)*.

A fetus responds to hypoxia by a so-called brain-sparing effect. This means redistribution of blood flow in favor of vital organs such as the brain, heart and adrenals at the expense of peripheral organs *(Jensen et al. 1999)*. The fetus reduces its oxygen consumption by reducing its intrauterine movements and breathing movements. However, if hypoxia develops gradually, the fetus will show adaptation and return to a normal activity level after several hours *(Koos et al. 1988, Bocking et al. 1988)*. The adaptation processes activated by the changed circumstances are controlled by the ANS. When uterine blood flow in a lamb was experimentally restricted long enough to cause fetal acidosis (mean pH = 7.0), agonal, preterminal FHR patterns emerged (mean heart rate 81 bpm; mean pH = 6.86) and the blood flow to the vital organs, which had increased initially, ultimately decreased profoundly *(Block et al. 1990)*. Thus, although the lamb fetus is able to modify its blood circulation even during severe hypoxia, prolonged anoxia leads to breakdown of the compensation mechanisms.

The initial reserves of the fetus to withstand variable hypoxic conditions during delivery cannot be measured and the individual´s compensatory capacity is tested during intrapartum stress.

Table 1. Fetal responses to hypoxia. FHR = fetal heart rate; FHRV = fetal heart rat variability; BP = fetal blood pressure; ↑,→= first increase, then return to baseline; ↑,↓ = first increase, then decrease; ↔ = no change; ↑ = increase; ↓ = decrease

	FHR	FHRV	BP	Intrauterine movements	Breathing movements	Redistribution of blood flow	Catechol-amines
Chronic hypoxia	↑,→	↔	↑,↓	↔	↔	yes	↑
Chronic hypoxia with an acute hypoxic event	↓	↑,↓	↑			yes	↑↑
Acute hypoxia	↓	↑	↑	↓	↓	yes	↑
Acute, prolonged hypoxia	↓	↓	↑,↓				

Table 2. Fetal response to oxygen deficiency.

HYPOXEMIA	HYPOXIA	ASPHYXIA
• more effective oxygen uptake, increase in hemoglobin level • reduced intrauterine movements • decreased growth rate • maintained energy balance	• surge of stress hormones • redistribution of blood flow • switch to anaerobic metabolism in peripheral tissues • maintained energy balance	• alarm reaction, all compensating systems in use • switch to anaerobic metabolism also in the central organs • heart failure ensues

2.2 Autonomic control of fetal cardiac function

2.2.1 Autonomic control of fetal heart rate

The ANS coordinates the cardiovascular system and adjusts functions to appropriate levels in stress situations. The heart is under the control of both the sympathetic and the parasympathetic nervous systems. The sympathetic nervous system has cardio-acceleratory effects, whereas the parasympathetic system has cardio-inhibitory effects (Table 3). Besides these neural control systems, there are also non-neural, humoral transmitters that augment the effect of neural transmitters. Catecholamines (noradrenaline, adrenaline, dopamine) are released from the adrenal medulla to augment the effect of the sympathetic nervous system, especially in stress situations. The parasympathetic nervous system influences the heart via the vagal nerve, which conducts impulses from the medulla oblongata in the central nervous system to the sino-atrial node in the fetal heart. The sympathetic nervous system has nerve fibers that terminate throughout the muscle of heart *(King et al. 2000)*. Although there are significant non-neural influences, it appears that a large proportion of FHRV may be explained by centrally mediated fluctuations of the ANS *(Oppenheimer et al. 1994)*. Further, an important determinant of FHRV is the actual FHR. Low FHRV associates with higher FHR as high FHRV appears with lower FHR *(Lange et al. 2005)*.

The role of the sympathetic and parasympathetic limbs of the ANS on the modulation of FHRV has been studied mostly in animal models under pharmacological manipulation. In ovine fetuses, parasympathetic (vagal) blockade with atropine reduces FHRV as FHR increases. Sympathetic blockade with propranolol does not change FHRV, although FHR decreases. When both limbs of the ANS are blocked, FHR increases and FHRV decreases dramatically, implying that ANS is directly responsible for a large part of FHRV. Still, the influence of non-neural systems persists, since some variability does remain after double blockade of the ANS *(Dalton et al. 1983)*. The findings in human fetuses are consistent with the experimental studies. Blocking the sympathetic nervous system by an injection of propranolol under the skin of the fetal scalp lowers FHR, while blocking the parasympathetic nervous system with atropine increases FHR *(Renou et al. 1969)*.

Table 3. Differences in the activation of the fetal autonomic nervous system.

SYMPATHETIC ACTIVATION	PARASYMPATHETIC ACTIVATION
• slower response	• fast response
• stress hormones	• vagal nerve
• increase cardiac contractility	• decrease in heart rate
• increase in heart rate	• blockade with atropine
• blockade with propranolol	

2.2.2 Maturation of autonomic cardiac control and heart-rate variability

The gestational age affects the control of ANS. The sympathetic control of the heart begins early in gestation. The parasympathetic system matures later and has only little effect on FHR prior to term gestation *(Walker et al. 1978)*. Experimental studies on ovine fetuses have identified functional cardiac adrenergic (sympathetic) control as early as on the 60th day of gestation (gestation averages 145 days), whereas preterm fetuses showed only little parasympathetic control of the heart. The effect of the parasympathetic control increases toward term, during the last third of gestation, but parasympathetic blockade with atropine in term fetuses raises FHR only with 10%. This observation suggests also that there is progressive maturation of parasympathetic control in late gestation, which probably extends through the early neonatal period *(Walker et al. 1978, Nuwayhid et al. 1975)*. Therefore, the sympathetic cardioaccelerating tone predominates over the parasympathetic cardioinhibitory tone during intrauterine life *(Assali et al. 1977)*. As the vagal activity increases as of the second trimester of pregnancy, FHR gradually decreases towards term *(King et al. 2000, Walker et al. 1978, Wakatsuki et al. 1992)*. The FHRV increases with advancing GA *(Wheeler et al. 1978, Ribbert et al. 1991a, Park et al. 2001)*.

As there is maturation of the neural control of the heart, there is maturation of non-neural cardiac control. As the fetus matures, it may become more responsive to increased humoral stimuli *(Nuwayhid et al. 1975)*. When lamb fetuses were exposed to acute hypoxia caused by complete occlusion of the maternal abdominal aorta for 60 seconds, there was a higher increase in noradrenaline levels in mature fetuses than immature fetuses. In mature fetuses also the T/QRS ratio in the fetal ECG peaked higher due to hypoxia and recovery rates were slower than in immature fetuses *(Widmark et al. 1989)*. These different cardiac responses are mainly related to the level of fetal maturation, and may be caused by changes in the ANS or by organ hypoxic reactivity. The increase in catecholamine levels after only short hypoxic periods

emphasizes the importance of the sympatheticoadrenal system for the maintenance of fetal hemodynamics during hypoxia *(Widmark et al. 1989)*.

2.2.3 Intrapartum factors affecting fetal autonomic cardiac control and heart rate variability

2.2.3.1 Fetal factors

FHR and FHRV are affected by fetal intrauterine movements and breathing. Accelerations in FHR are mostly associated with fetal movements, and can occur with or without a contraction *(Dawes et al. 1981, Sadovsky et al. 1984)*. Growth-retarded fetuses have lower increase in FHRV as a response to intrauterine movements than control fetuses *(Breborowicz et al. 1988)*, which may be due to diminished reserves of cardiovascular control in fetuses with growth retardation.

In mature fetuses before labour, fetal breathing movements are related to reduced FHR and increased beat-to-beat FHRV *(Dawes et al. 1981, Divon et al. 1985)*. During labor, fetal breathing decreases and the fetus makes breathing movements only during about 1% of the time *(Boylan et al. 1980)*. The intrauterine movements of the fetus are also reduced during labor, especially if hypoxia is present *(Natale et al. 1981, Kozuma et al. 1997)*.Thus, breathing movements and other movements are unlikely to interfere substantially with the interpretation of FHRV during delivery.

2.2.3.2 Hypoxia

Hypoxia induces changes in FHR and FHRV which are controlled by the ANS, along with chemoreceptors, baroreceptors, increased secretion of catecholamines and higher cortical functions in the brain *(King et al. 2000, Rosén et al. 1984, Jones et al. 1975)*. The importance of adequately functioning cardiovascular control systems has been shown in a study with ovine fetuses whose both carotid chemoreflexes and release of catecholamines were blocked. The survival of these fetuses during hypoxia was substantially reduced *(Giussani et al. 1993)*.

Hypoxia increases the activity in parasympathetic efferent vagal fibers to the heart and induces bradycardia. This is a marker of an adequate compensating mechanism, as the energy demand on the heart decreases and helps the fetus to cope with hypoxia. However, after a hypoxic episode, increased sympathetic activity may rapidly increase FHR and FHRV (overshoot acceleration) *(Bennet et al. 2009)*. Fetuses which are stressed at the outset and have increased catecholamine levels might not be able to compensate for acute hypoxic events, as implied by the finding that the FHR of such fetuses returned to control values after an initial period of bradycardia. These fetuses had more marked acidosis compared to fetuses with sustained bradycardia during the whole (one-hour) study period *(Jones et al. 1975, Giussani et al. 1993)*.

A reduction in FHRV in the presence of bradycardia appears to be a rather late sign of severe acidosis *(van Ravenswaaij-Arts et al. 1993, Ribbert et al. 1991b)* and is

associated with reduced cerebral oxygen consumption and poor fetal outcome *(Williams et al. 2002, Field et al. 1991)*. Overall, the amount and direction of hypoxia-induced changes in FHR and FHRV depend on the initial status of the fetus, and also on depth and duration of the hypoxic episode.

2.2.3.3 Contractions

Uterine contractions affect FHR by temporarily reducing or stopping cord blood flow, increasing fetal blood pressure and thus affecting ANS. During contractions, FHR increases or decreases, depending on the fetal status. In a healthy, non-stressed fetus, FHR may remain unchanged during contractions. A marked increase in FHR is noted during contractions in the presence of fetal body movements. After a contraction, FHRV returns to the baseline level. This happens regardless of fetal movements. An increase in FHRV during contractions may be due to mild hypoxia or increased vagal tone *(Zimmer et al. 1987, Zimmer et al. 1988, Divon et al. 1984, Romano et al. 2006)*. Increased FHR and FHRV during a contraction is a sign of adequate fetal reactivity to uterine pressure stimulus and marks fetal wellbeing *(Divon et al. 1984)*.

Compared to non-laboring women, FHRV is overall greater during labor in fetuses with a reassuring CTG pattern *(Agrawal et al. 2003)*. In the course of labor, the long-term variation of FHR increases *(Pello et al. 1991)*, although with more frequent, longer, and intense contractions, FHRV may decrease *(Zimmer et al. 1998)*; this may be due to an aggravation of hypoxemia with more intense contractions.

2.2.3.4 Labor analgesia

Labor analgesia may affect the FHR. Paracervical analgesia is safe and affects neither the FHR nor fetal oxygenation *(Kaita et al. 2000)*. In contrast, intrathecal or epidural analgesia may affect the FHR, but any changes are minimal as long as the mother does not have hypotension or uterine hypertonia. Effective labor analgesia decreases adrenaline levels in the painful parturient. As adrenaline has a tocolytic effect, rapid labor pain relief might increase uterine activity, which would be beneficial for parturients with slowly progressing labor. Intrathecal analgesia may cause uterine hyperreactivity, especially if the parturient also receives oxytocin *(Palmer et al. 1999, Capogna 2001)*.

In a study of 200 patients on epidural or intrathecal analgesia, 22 had significant FHR changes. In four patients, the changes suggested improved fetal status. Eighteen patients had FHR abnormalities (decelerations or bradycardia), but none required urgent delivery because of these changes. Nonetheless, the incidence of FHR changes was low (6% in the epidural group and 12% in the intrathecal group), and all changes were transient and resolved within 30 minutes *(Palmer et al. 1999)*. Overall, labor analgesia decreases maternal stress and circulating catecholamine levels, corrects possible maternal metabolic acidosis if present, and may thus improve uteroplacental perfusion. Epidural analgesia improves the fetal acid-base balance at birth *(Reynolds 2011)*.

2.3 Intrapartum fetal monitoring

2.3.1 Cardiotocography

Cardiotocography records FHR changes and their temporal relationship to uterine contractions. The aim of intrapartum monitoring is to identify fetuses that are becoming hypoxic, and to prevent an adverse outcome. A normal FHR tracing during labor predicts a well-oxygenated neonate with a normal acid-base balance. However, CTG has several limitations: the positive predictive value of abnormal intrapartum FHR patterns for fetal acidemia is only around 30 %, and continuous CTG monitoring may increase unnecessary operative interventions *(Spencer 1993, Alfirevic et al. 2006)*. The FHR tracings are interpreted visually, i.e. subjectively, which leads to high interobserver variability, especially of nonreassuring tracings. There is a lack of agreement on how to classify most abnormal features of the FHR tracing *(Chauhan et al. 2008)*, while the agreement among is better concerning normal tracings (kappa value = 0.86, total agreement gives a kappa value = 1.0) *(Blix et al. 2003)*.

Continuous electronic fetal monitoring has been criticized for an inability to decrease fetal mortality and cerebral palsy and for increasing the incidence of unnecessary operative deliveries. Nevertheless, the technique is still widely used as a routine method for fetal surveillance intra partum: in some countries at least 85 % of births are monitored with CTG *(Bailey 2009)*.

Automatic computerized analysis of the FHR pattern during labor may be a method for improving the accuracy and consistency of detecting specific FHR patterns *(Dawes et al. 1994, Parer et al. 2010)*. It provides a precise and reproducible algorithm-based approach to FHR analysis. Different FHR variables (baseline, variability, accelerations and decelerations), together with the incidence of fetal movements, can be measured. Long-term FHRV is defined as the mean of a one-minute range of pulse intervals and short-term FHRV as the mean of successive epochal (1/16 min; 3,75 s) pulse interval differences. The results of the analysis are given on-line *(Dawes et al. 1994)*. Different analysis devices measure different variables. FHR tracings have been successfully used for computerized analysis of FHRV before labor *(Dawes et al. 1992)*. Unfortunately, this analysis has not proved helpful during labor, since there has been no correlation between FHR variables and fetal acidemia at birth. Overall, the predictive value of various features of FHR tracings with regard to fetal acidemia is poor *(Agrawal et al. 2003, Pello et al. 1991, Parer et al. 2006, Schiermeier et al. 2008)*. Altogether, the FHR pattern offers only a partial picture of the fetal status, and new methods are needed to identify fetuses at risk for acidosis.

2.3.2 Fetal scalp blood pH

Fetal scalp blood sampling is used as a golden standard to identify intrapartum fetal hypoxia. CTG can be used for screening tool; FBS is taken under certain conditions when the CTG is nonreassuring *(NICE Clinical Guideline 2007)*. The pH-value falls, when the acidity of the body fluids increases as a consequence of accumulation of lactic

acid due to metabolic acidosis *(Parer 1980)*. Since acidosis is a key feature of fetal asphyxia, a decreasing pH-value indicates fetal distress and a risk of permanent tissue damage. A low pH and accumulation of lactic acid are due to oxygen and caloric deficit in tissues and are related to perinatal brain damage *(Fleischer et al. 1982)*.

There are only few contraindications to FBS. They are: certain maternal blood-borne infections (hepatitis, human immunodeficiency virus, active maternal herpes simplex), fetal bleeding disorder, and fetal prematurity (< 34 weeks of gestation) *(Heazell et al. 2011)*.

FBS gives only momentary information of fetal wellbeing (concerning oxygenation), and needs often to be taken repeatedly. FBS is time-consuming and inconvenient to the parturient and may lead to complications, e.g. fetal scalp infection and hemorrhage. The incidence of complications ranges from 0.4 to 6 % Most complications due to FBS are insignificant, although exceptional cases of neonatal death due to bleeding from the incision wound have been reported *(Sabir et al. 2010, Schaap et al. 2011)*. There is no correlation between fetal scalp pH and neonatal outcome *(NICE Clinical Guideline 2007)*. There are many confounding factors, e.g. air or amniotic fluid contamination or congestion of the fetal scalp which may affect the result. In prolonged labor, maternal acidosis may develop: as acid equivalents cross the placenta fetal capillary pH is reduced. All these matters should be kept in mind when using FBS to interpret fetal wellbeing during labor *(Mahendru et al. 2011)*. In a Cochrane Review *(Alfirevic Z et al. 2008)*, the use of FBS was questioned: There was no evidence that the incidence of caesarean section rate was greater in trials where FBS was not available. Moreover, access to FBS data did not appear to influence the occurrence of neonatal seizures nor any other specified outcome.

2.3.3 STAN®

Fetal hypoxia alters the shape of the ECG tracings and technical systems to monitor the ECG of the fetus have been developed *(Neilson 2006)*. The ST waveform of the fetal ECG provides continuous information on the metabolic status of the heart and the ability of the fetal heart muscle to respond to decreased oxygenation caused by the stress of labor. Fetal ECG is recorded during labor with a spiral electrode attached to the scalp of the fetus. The STAN® (ST ANalysis; Neoventa Medical, Mölndal, Sweden) monitor analyses the ST segment of fetal ECG as an adjunct to a standard CTG. The ratio between the amplitudes of the T waves and QRS complexes (T/QRS) is quantified. An increase in the height of the T wave occurs in hypoxia when the energy balance becomes negative and glycogen reserves in the heart are used anaerobically for extra energy. A change in the T/QRS ratio compared to an earlier T/QRS ratio is called an ST event in the STAN® nomenclature. The significance of this ST event is evaluated according to STAN® clinical guidelines *(Amer-Wåhlin et al. 2011)*. The indications for using STAN® are: need for more detailed fetal surveillance (high-risk pregnancies), possible or clearly abnormal external CTG, induced or oxytocin-enhanced labor, meconium-stained amniotic fluid. The gestation time needs to be over 36 weeks, the membranes need to have ruptured and no contraindications against invasive monitoring may be present *(Luttkus et al. 2004, Devoe 2011)*.

A drawback of this method is that the CTG tracing must be correctly classified before STAN® if the recommended action is to be the correct one *(Amer-Wåhlin et al. 2007)*. Nevertheless, a recent Cochrane Review concludes that monitoring the fetus using CTG plus ST waveform analysis results in fewer fetal blood samples (risk ratio [RR] = 0.61), fewer operative vaginal deliveries (RR = 0.90) and fewer admissions to special care units (RR = 0.89) in comparison to CTG monitoring alone *(Neilson 2012)*. According to a meta-analysis on ST analysis of fetal ECG *(Becker et al. 2012)*, the additional use of ST analysis reduces also the overall incidence of operative deliveries. The incidence of metabolic acidosis was reduced in most randomized studies, but was not statistically significantly less than when ST analysis was used (RR = 0.72, confidence interval 0.43–1.19). However, by Cochrane way of analysis, the reduction in the occurrence of metabolic acidosis was significant.

To overcome the problems of subjective interpretation of CTG, Costa et al. used a computerized system which analyses the features of the CTG tracings as well as the ST changes. This method may improve the predictability of neonatal acidemia (cord pH ≤ 7.05), but the result is handicapped by a small number of acidotic fetuses *(Costa et al. 2009)*. Thus, computerized monitoring systems which analyze various parameters of the CTG and the ECG might help to identify intrapartum fetal acidosis more accurately than CTG alone.

2.4 Power spectral analysis

2.4.1 Analysis of FHRV by power spectral analysis

The fetal heart rate oscillates at specific frequencies, and the duration of the R-R interval changes continuously around a mean value, as the negative feedback and time-delay of the cardiovascular control system operate *(Akselrod et al. 1981, Malliani et al. 1994a)*. Power spectral analysis is used to investigate the frequency content of heart rate fluctuations, and to estimate the effect of neural regulation on heart rate patterns *(Verklan et al. 2004, Kwon et al. 2011)*. An advantage of spectral analysis for studying heart rate variability is that the amount of variability and the oscillation frequency can be quantified simultaneously. A series of sequential R-R intervals from ECG data are decomposed into a sum of sinusoidal functions of different amplitudes and frequencies by a fast Fourier transform algorithm. This makes unseen, minute changes in FHRV objectively detectable *(Verklan et al. 2004)*.

When heart rate variability is decomposed in the frequency domain by spectral analysis, the relationships among various frequency components and specific control processes can be established *(Groome et al. 1994)*. The low-frequency (LF) spectral band, which stretches from 0.04 Hz to 0.15 Hz (from 2.4 to 7.8 cycles / min), corresponds mainly to sympathetic and parasympathetic control, and the high-frequency (HF) band, from 0.15 Hz to 1.0 Hz (from 7.8 to 60 cycles / min), corresponds to parasympathetic control *(Anonymous1996)*. The mid-frequency (MF) band, which resides between the LF and HF bands, may be calculated separately; this spectral band is thought to relate to the baroreceptor reflex *(Li et al. 2004, Chatow et al. 1995)*.The

very low-frequency (VLF) band (< 0.04 Hz) is not usually used when short-term recordings are interpreted, since the physiological basis for the VLF band related to FHRV is not well understood, and may, in fact, be questionable. The low-to-high frequency ratio (LF/HF) is assumed to reflect the sympatho-vagal balance *(Anonymous1996, Malliani et al. 1994b)*.

Autonomic cardiac control matures with advancing GA, as verified by analyses of the spectral powers of FHRV. Ferrazzi et al. found that the HF spectral power (corresponding to vagal cardiac control) was not present at 26 weeks of gestation, but was evident at 36 weeks of gestation *(Ferrazzi et al. 1989)*. Overall, both the LF and the HF spectral powers increase and the LF/HF ratio diminish with advancing GA. This indicates greater parasympathetic control as the fetus matures *(Van Leeuwen et al. 2003)*. Besides GA, the spectral powers of FHRV are also affected by fetal behavioral patterns, at least before labor *(Visser et al. 1982)*.

2.4.2 Spectral analysis of FHRV in detecting fetal acidosis

The way in which fetal oxygen deficiency affects the spectral powers of FHRV has been studied by different procedures and methods and at various spectral bandwidths.

Acute oxygen deficiency in ovine fetuses has been induced by occluding the maternal abdominal aorta, by decreasing maternal inspired oxygen, and by embolization of the placenta. The experimental studies on the effect of fetal hypoxia on spectral analysis of FHRV are summarized in Table 4. In acute hypoxemia, all spectral powers of FHRV increase. During a 10-minute recovery after induced hypoxemia HF spectral powers increase compared to LF powers, suggesting increased parasympathetic activity during recovery *(Yu et al. 1998, Min et al. 2002)*. Acute hypoxia and acidosis induced by repeated umbilical artery embolism (three times at an hourly interval; fetal pH decrease from 7.33 to 7.08) causes a decrease in FHR. All spectral powers increase significantly over baseline values during the study period; the highest increase occurs in the VLF and LF bands *(Li et al. 2004)*. This indicates that fetuses in distress react to acute hypoxemia by increasing their autonomic drive.

There are only a few clinical studies published on the association between FHRV as assessed with spectral analysis and fetal hypoxia during labor *(Kwon et al. 2011, Chung et al. 2001, Salamalekis et al. 2006, van Laar et al. 2010)*. These studies are summarized in Table 5. The study periods, definitions of hypoxemia and acidosis, and the ranges of spectral bands used vary among the studies. Hypoxemia (cord artery pH < 7.15 or < 7.20) seems to increase VLF, LF and MF spectral powers, although there are also contradictory findings. Chung et al found that the LF power decreases two hours before delivery in hypoxemic fetuses *(Chung et al. 2001)* and that there is no change or a decrease in the HF spectral power. The LF/HF ratio rises, but this has been measured in only one study *(Kwon et al. 2011)*. Acidotic fetuses (cord pH < 7.05) have been studied only in one study *(van Laar et al. 2010)*. Laar et al found that during the last 30 minutes of labor, there is no difference in LF or HF powers between acidotic and control fetuses. However, the relative LF power (LF per total power) was significantly increased, and the relative HF power decreased in the hypoxic group.

Although the results vary by study protocol, fetal responses to oxygen deficiency and changed circumstances are reflected in the changed balance of spectral powers of FHRV, with as a slight shift towards sympathetic predominance.

Table 4. Spectral powers of fetal heart rate variability and hypoxia. Experimental studies on ovine fetuses.

Author Publ. Year	n	Spectral analysis method	Study period	Level of oxygen deficiency	Effect of oxygen deficiency
Lindecrantz *et al.* 1993	7	Autoregression	200 beat-to-beat segment prior and after 60 s of occlusion of the maternal aorta	hypoxemia (oxygen tension drop from 2.2 to 1.2 kPa) modest change in pH	- VLF (~0.00Hz) disappeared due to hypoxemia - LF (~0.065Hz) markedly increased - HF (~0.50Hz) peak appeared after hypoxemia
Yu *et al.* 1998	7	FFT (pulse interval measured from arterial pressure wave)	100 s segments; 2 before, 7–8 during, and 2 segments after hypoxia (maternal oxygen deficiency)	PO_2 12–14.5 mmHg (mild hypoxemia) PO_2 10–11.9 mmHg (moderate hypoxemia); no pH changes	- Spectral power from 0.04 to 0.45Hz increased due to mild and moderate hypoxemia
Min *et al.* 2002	8	Smoothed power spectral analysis	60 s segment before, during and after 60 s of occlusion of the maternal aorta	Pa O_2 decreased (hypoxemia); no change in pH	- LF (0.04–0.15 Hz), HF (0.4–1.5Hz) and LF/HF increased due to hypoxemia
Li *et al.* 2004	7	Autoregression (pulse interval measured from arterial pressure wave)	2 min before and after 3 placental embolisms at hourly intervals (0h, 1h, 2h)	PO_2 fell by 50% pH decreased from 7.33 to 7.08 acidosis	- VLF (0.01–0.025 c/b) and LF (0.025–0.125 c/b) increased markedly due to hypoxia - MF (0.125–0.20 c/b) and HF (0.20–0.50 c/b) increased - rel VLF and rel LF decreased - rel HF increased

Publ. Year=publication year; s= seconds; min=minute(s); h=hour(s); FFT= fast Fourier transform; c/b=cycle/beat (can be converted to Hz by dividing with the average R-R interval); rel= relative power i.e. power divided with total power

Table 5. Spectral powers of fetal heart rate variability and hypoxia. Clinical studies on human fetuses.

Author Publ. Year	n (GA)	Spectral analysis method	Intrapartum study period	Level of oxygen deficiency	Effect of oxygen deficiency
Chung *et al.* 2001	40 (34-41w)	FFT	2 hours before delivery	Hypoxia: pH <7.15 + BE< -8mM/l (n=14) Distress: Abnormal CTG + apH>7.15 (n=26)	- VLF (<0.04 Hz) increased due to hypoxia - LF (0.04-0.15 Hz) and HF (0.15-0.4 Hz) decreased due to hypoxia - LF/HF: no change
Salamalekis *et al.* 2006	18 (>37w)	Matching pursuit	Second stage of labor	Hypoxemia: non-reassuring CTG and pH < 7.20	- VLF (<0.04 Hz) and LLF (0.04-0.08 Hz) increased due to hypoxia - LF (0.08 -0.15 Hz) and HF (>0.15 Hz): no significant change
van Laar *et al.* 2010	10 (>36w)	FFT	Last 30 min of labor and 3 to 2 hours before birth; values in 5min intervals	Acidosis: apH<7.05	- LF (0.04-0.15 Hz) and HF (0.4-1.5 Hz): no difference between acidotic and control groups - rel LF increased due to hypoxia - rel HF decreased due to hypoxia
Kwon *et al.* 2011	39 (> 37w)	FFT (FHR measured with US)	Last 2 hours of delivery, segment of 256 beats	Hypoxemia: apH <7.20	- Total (0.04-1.0 Hz), LF (0.04-0.15Hz) and MF (0.15-0.5Hz) increased due to hypoxemia - HF (0.5-1.0 Hz) and LF/ (MF+HF): no significant change - LF/HF increased due to hypoxia - rel LF and rel HF: no significant change

Publ. year=publication year; GA= gestational age at weeks; FFT= fast Fourier transform; US=ultrasound; apH= umbilical artery pH; BD=base deficit; VLF=very low frequency; LF=low frequency; MF=mid frequency; HF=high frequency; rel= relative power i.e. power divided with total power

3. AIMS OF THE STUDY

The aim was to investigate the effect of intrapartum acidosis on spectral powers of FHRV in term human fetuses. We hypothesized that, since power spectral analysis of FHRV measures changes in the autonomic nervous control of FHRV, power spectral analysis might detect fetal acidosis earlier and more accurately than CTG and STAN®, and that power spectral analysis could thus be used to monitor fetal wellbeing during labor and delivery.

The specific aims were to study:

1. whether intrapartum spectral powers of FHRV could be used for identifying fetuses at risk for birth acidosis.

2. whether changes in spectral powers of FHRV at the time of significant ST events in the fetal ECG are associated with fetal metabolic acidosis.

3. whether spectral powers of FHRV are associated with intrapartum FBS pH-values measured at the same time as the power spectral analysis is made.

4. SUBJECTS AND METHODS

4.1 Study design and subjects of studies I-IV

STUDY I

This preliminary study included 14 singleton fetuses with a GA exceeding 35 weeks delivered at the Turku University Hospital. Fetal R-R interval data was recorded with STAN® (Neoventa Medical, Mölndal, Sweden) for 15 minutes at a median of two hours before delivery. One two-minute, stable, noise-free signal segment was selected for power spectral analysis. Umbilical cord blood samples were obtained immediately after birth. The fetuses were divided into two groups: those with a cord artery BD value < 8 mmol/l (n = 8) and those with a cord artery BD value 8-12 mmol/l (n = 6) at birth.

The spectral powers of FHRV were compared between the groups, and the correlation between spectral powers and BD values was calculated.

Study groups	Studied FHR period	Main outcome measure
1) Cord BD < 8 mmol/l (n=8) 2) Cord BD 8-12 mmol/l (n=6)	2 min segment at a median of 2 hours before delivery	Intergroup FHRV difference Correlation between spectral powers of FHRV and cord BD values

STUDY II

The study comprised 334 fetuses with a GA exceeding 35 weeks. Data was collected from 12 Nordic delivery units as a part of a Nordic observational multicenter study *(Amer-Wåhlin et al. 2002)*. Fetal ECGs were recorded during the active phase of labor, and the umbilical cord acid-base status was measured after birth. The fetuses were divided into two groups according to their cord arterial acid-base status: 1) acidotic fetuses with a pH < 7.05 (n = 15) and 2) non-acidotic fetuses with a pH ≥ 7.05 (n = 319).

The spectral powers of FHRV from the last hour of delivery were assessed in 2-minute signal segments and the change in spectral powers between the study groups was measured. The association between spectral powers from the study period and cord pH was also measured.

Study groups	Studied FHR period	Main outcome measure
1) Cord pH < 7.05 (n=15) 2) Cord pH ≥ 7.05 (n=319)	Last hour of intrapartum fetal ECG recording	Changes in spectral powers of FHRV in the course of delivery between the study groups Association between spectral powers and cord pH

STUDY III

This was a case-control study with 34 fetuses, all with a significant ST event in the fetal ECG. Data was collected from ten European labor wards as a part of a European multicenter project on intrapartum fetal monitoring *(Luttkus et al. 2004)*. Twenty-two fetuses were acidotic (cord arterial pH $\leq$ 7.05) and 12 fetuses were not (cord pH $\geq$ 7.20). The median LF/HF ratio of FHRV was measured within a period of one hour before and one hour after the significant ST event. Spectral powers were measured in 2-minute signal segments.

The relative change in the LF/HF ratio [(median LF/HF_{after} - median LF/HF_{before})/ median LF/HF_{before}] at the time of the ST event was calculated. The magnitude of change in spectral powers was analyzed in order to establish a cut-off value to distinguish fetuses with metabolic acidosis at birth (pH $\leq$ 7.05 and BD $\geq$ 12 mmol/l) from fetuses with no acidosis at birth.

Study groups	Studied FHR period	Main outcome measure
All fetuses had a significant ST event in fetal ECG 1) Cord apH $\leq$ 7.05 (n=22) 2) Cord apH > 7.05 (n=12)	One hour before and one hour after a ST event	Change in LF/HF ratio in relation to a significant ST event Prediction of birth acidosis

STUDY IV

This was a retrospective study with 462 fetuses who had a normal pH-value (pH > 7.20; controls) in a scalp blood sample and 81 fetuses who had a low pH-value (pH ≤ 7.20; low-FBSpH-fetuses). The fetuses for this study were selected from the same data base as those for Study III *(Luttkus et al. 2004)*. The low-FBSpH-fetuses were further divided into two subgroups according to the degree of acidemia: fetuses with FBS pH 7.11–7.20 (n = 58) and fetuses with FBS pH ≤ 7.10 (n = 23).

Two additional groups with two measure points during delivery were chosen: in the first group (108 fetuses), both the first and the last FBS pH were normal, and in the second group (40 fetuses) the initial FBS pH was or the 30 min CTG segment at the beginning of the recording was normal but the last-FBS pH-value was low (pH ≤ 7.20).

FHRV was measured in 2-minute segments from a 14-minute period prior to FBS. The intergroup difference in spectral powers of FHRV between the controls and low-FBSpH-fetuses and between the subgroups were measured. The correlation between spectral powers and the concomitant FBS pH-value was calculated to examine how FHRV associates with fetal intrapartum pH-values. Further, the change in spectral powers of FHRV during labor was assessed in fetuses with repeatedly normal FBS pH-values, and in fetuses with a low last-FBS pH-value.

Study groups	FHR period studied	Main outcome measure
1) FBS pH > 7.20; (n=462) 2) FBS pH ≤ 7.20; (n=81) • FBS pH 7.11–7.20 (n=58) • FBS pH ≤ 7.10 (n=23)	14 min preceding last FBS 14 min preceding first FBS or 30 min during normal CTG	Association between spectral powers of FHRV and concomitant FBS pH-value Intergroup difference in FHRV Change in spectral powers in the course of delivery

4.2 Data acquisition and signal processing

The fetal ECGs was recorded during delivery with an intrauterine scalp electrode attached to presenting part of the fetus using a STAN® monitor (Cinventa Ab, Mölndal, Sweden; Study I) and a STAN®S 21 monitor (STAN®, Neoventa Medical, Mölndal, Sweden; Studies II-IV) (Figure 2). The fetal unipolar ECG lead configuration consisted of a single-helix scalp electrode and a maternal skin electrode. STAN® provides the averaged QRS complex and an instantaneous plot of each R-R interval at a resolution of 2 ms *(Rosén et al. 1989)*. R-peaks were detected, and R-R intervals were measured and digitized at a sampling rate of 500 Hz (1000 Hz in Study I). The R-R interval data sets were stored digitally as part of STAN® data archiving, and the intervals from the study period were analyzed off-line. The R-R interval data sets were transformed to a continuous digital signal by linear interpolation, and then the event series was resampled at the rate of 16 Hz. The reciprocal of each R-R interval was computed to obtain the respective instantaneous heart-rate reading. The data was analyzed in 2-minute segments. In the case of large signal breaks in this R-R data segment, a new segment was started immediately after a break to minimize loss of data.

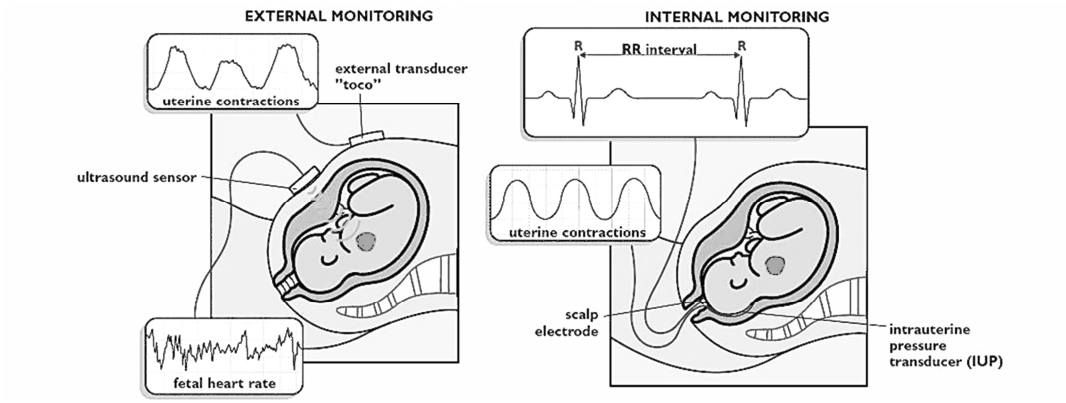

Figure 2. Left: Cardiotocogram. Right: Intrauterine scalp electrode to register the electrocardiogram and R-R interval, and an intrauterine pressure analyzer to measure contractions. (©Neoventa Medical AB, with permission)

4.3 Power spectral analysis

The FHRV was measured with power spectral analysis in 2-minute signal segments. The quality of these segments was checked by a signal analyst, and data analysis was performed with no knowledge of the clinical data. Fast-Fourier-transformed power spectra were computed for the FHR signal segments (MATLAB®-oriented tailor-made signal analysis - program, MARAPS, Tampere, Finland) *(Välimäki et al. 1999)*.

In the preliminary study (Study I), a slightly wider frequency band was used than in the subsequent studies. The frequency at outset was 0.03 Hz. Three spectral bands were

calculated: low-frequency (LF; from 0.03 Hz to 0.07 Hz), mid-frequency (MF; from 0.07 Hz to 0.13 Hz), and high-frequency (HF; from 0.13 Hz to 1.0 Hz). In Studies II-IV, the FHRV spectrum was integrated over the total frequencies from 0.04 to 1.0 Hz. The LF band was integrated over frequencies from 0.04 Hz to 0.15 Hz, and thus included most of the mid-frequency band used in Study I. The HF band was from 0.15 Hz to 1.0 Hz. The LF/HF ratio was calculated. All data on spectral variability are presented in arbitrary units (AU).

To minimize the effect of FHR on FHRV, the coefficient of component variance (square root of power spectra / mean R-R interval) was calculated *(Hayano et al. 1990)*.

4.4 Statistical analysis

Study I: The intergroup difference was tested with a Mann-Whitney U-test. The correlation between the spectral powers and BD values was calculated by the Spearman correlation test, where r = 1.0 represents perfect correlation.

Study II: Longitudinal data of FHR and FHRV parameters from the last hour of recording were analyzed with analysis of variance (ANOVA) for repeated measures, where the grouping factor (acidotic or control) and the within factor (time of study period) were independent variables. Because the distribution of the data was skewed, the FHRV values were log-transformed for repeated measures analysis (excluding FHR). If there were significant interactions between the group and time of study period, Student's *t* test was used for further analysis. The association between FHR or FHRV (dependent variables) and gestational age, birth weight, and cord arterial pH-value (continuous independent variables) was analyzed with the linear model for repeated measures. The time of the study period was used as the repeated factor in the linear models.

Study III: For each fetus, a relative change in the LF/HF ratio was calculated [(median LF/HF_{after} - median LF/HF_{before})/ median LF/HF_{before}] in association with an ST event. The best cut-off value to identify fetuses with metabolic acidosis at birth was determined by a receiver operating characteristic (ROC) curve. Logistic regression analysis was used to test whether the same cut-off value could be used for both an increase and a decrease in the LF/HF ratio.

Study IV: The associations between spectral powers and FBS pH-values were analyzed with the Spearman Partial Correlation coefficient test. As GA is known to affect FHRV *(Assali et al. 1977)* and spectral powers *(van Laar et al. 2009)*, GA was used as a covariate when calculating the correlation between spectral powers and the FBS pH- value. The differences of the spectral powers between the subgroups were tested with the *t*-test.

The clinical data were analyzed with Student's *t*-test, Wilcoxon's two-sample test or Fisher's exact test, as appropriate. The results are expressed as mean (range) or median [range], as appropriate (Studies II, III and IV).

A *P*–value < 0.05 was considered significant. Statistical analyses were performed with the SAS System for Windows, release 8.01 (SAS Institute, Cary, North Carolina, USA).

5. RESULTS

5.1 Spectral powers of FHRV during labor, and in relation to umbilical cord acid-base status (Studies I and II)

In Study I, the MF spectral powers correlated inversely with cord artery BD (r = -0.6; p = 0.02). The total and MF FHRV of fetuses with mild metabolic acidosis (cord BD 8-12 mmol/l) at birth was reduced (p = 0.01 in both comparisons) at a median of 2-hours (1–8 h) before delivery (Figure 3). The changes in FHRV were no accompanied by changes in the mean heart rate.

In Study II, fetuses that were acidotic at birth (cord pH ≤ 7.05) had a higher LF/HF ratio of spectral powers than non-acidotic fetuses (p = 0.002) during the last hour of intrapartum monitoring. The LF, HF and total spectral powers of FHRV gradually increased in the acidotic fetuses, but then dropped near delivery (Figure 4). Total and LF spectral powers and the LF/HF ratio were inversely associated with cord pH-values (p < 0.001; p < 0,001; p = 0.007; respectively). In summary, hypoxia increases initially spectral powers of FHRV, and the FHRV decreases as acidosis becomes more pronounced.

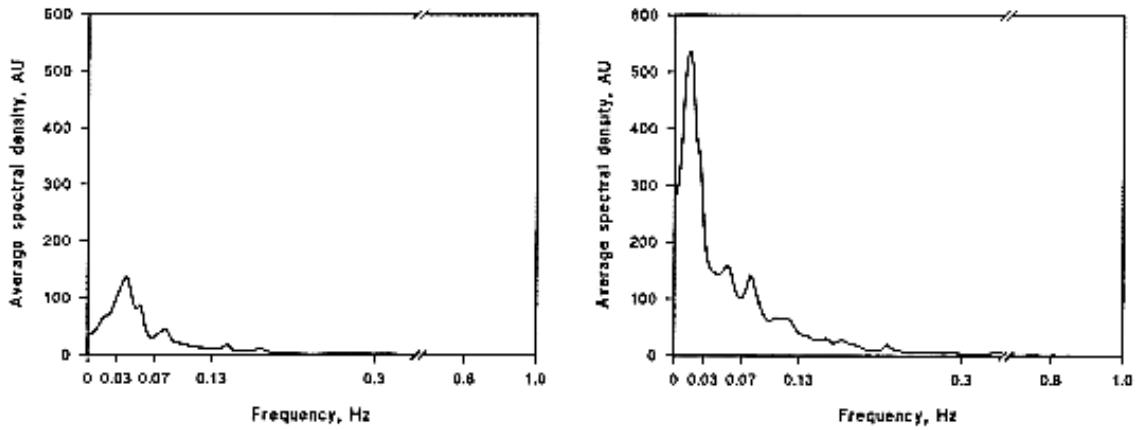

Figure 3. Left: FHRV spectral powers of eight fetuses with cord arterial BD values 8-12 mmol/l. Right: Spectral powers of six fetuses with BD < 8 mmol/l. The fetuses with BD 8-12 mmol/l had significantly lower total (0.03-1.0 Hz) and mid-frequency (0.07-0.13 Hz) spectral powers of FHRV (p = 0.01). (AU = arbitrary units). (Study I)

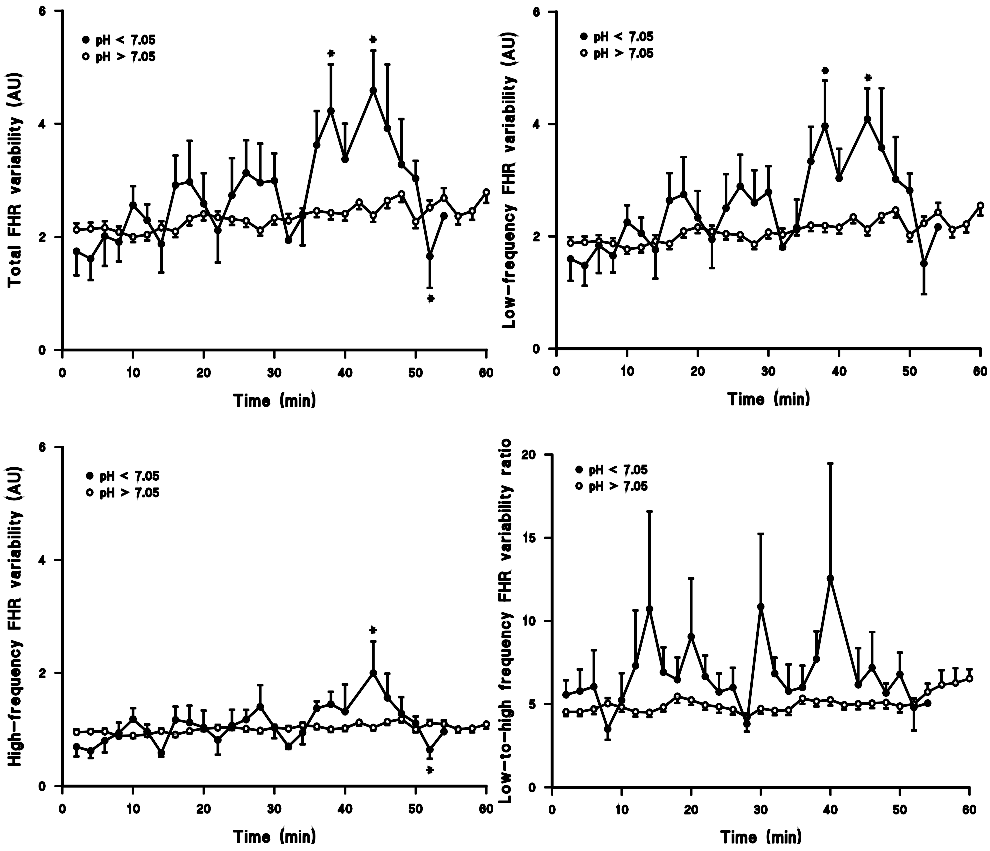

Figure 4. FHRV during the last hour of labor in acidotic (pH < 7.05) and non-acidotic (control) fetuses (pH ≥ 7.05). There was a significant interaction between the study groups and time of the study period in total (P = 0.018), LF (P = 0.03) and HF FHRV (P = 0.009; ANOVA for repeated measures). The LF/HF ratio was greater in the acidotic group (P = 0.002) and there was no significant interaction. The spectral powers of FHRV are presented in arbitrary units (AU). * = significant difference between groups (P < 0.05; two sample t test). (Study II)

5.2 Intrapartum spectral powers of FHRV in relation to fetal scalp pH (Study IV)

Fetuses with FBS pH ≤ 7.20 (intrapartum hypoxia) had increased spectral powers of FHRV compared with controls (FBS pH > 7.20) (p = 0.038). Interestingly, the fetuses with the lowest FBS pH (≤ 7.10) had significantly lower spectral powers when compared to fetuses with FBS in the pH-range 7.11-7.20 (p = 0.047) (Figure 6). On the whole, the individual variance of spectral powers was wide (Figure 5). In the process of labor and delivery, fetuses developing intrapartum hypoxia (normal first scalp pH-value or normal CTG, and last scalp pH-value ≤ 7.20) had a more pronounced increase in

spectral powers of FHRV from the first to second measure points when compared with fetuses with repeatedly normal scalp pH-values (> 7.20) (p = 0.0005).

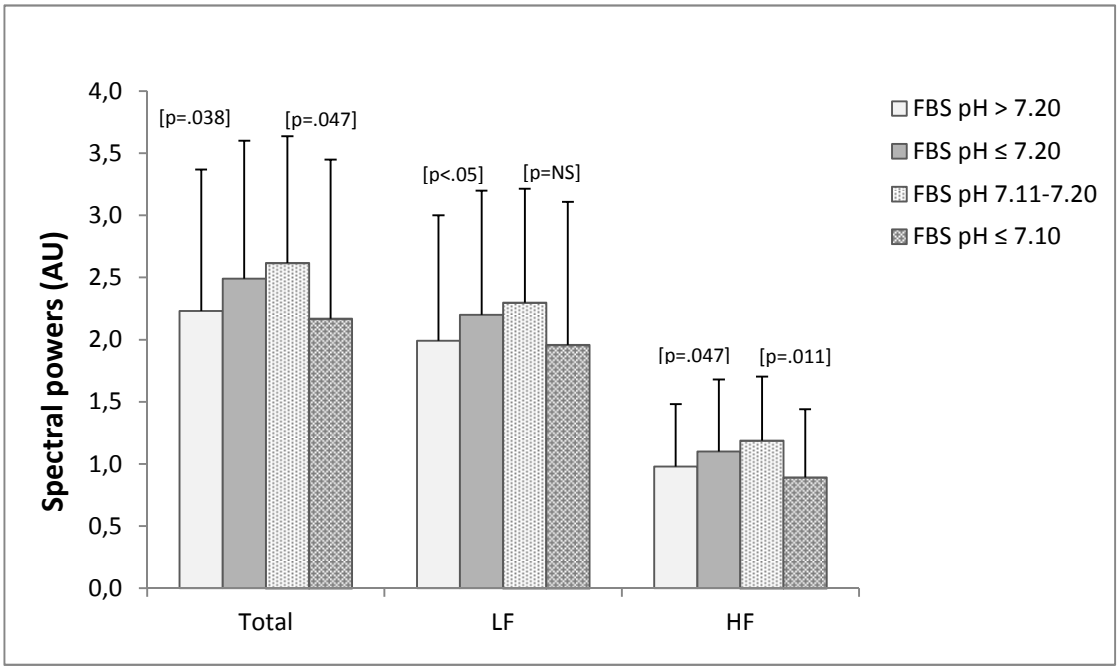

Figure 5. Total, LF, and HF spectral powers of FHRV in control fetuses (scalp pH > 7.20), and in fetuses with a low pH in FBS (pH ≤ 7.20), and in subgroups with FBS pH 7.11-7.20 and FBS pH ≤ 7.10. p-values are presented between the controls and low-FBS-fetuses, and between the subgroups. Mean spectral values are in arbitrary units (AU). (Study IV)

5.3 Correlation between FHRV and intrapartum FBS pH-values (Study IV)

Total spectral powers of FHRV of low-FBSpH-fetuses (pH ≤ 7.20) correlated positively with the concomitant FBS pH (r = 0.29; p = 0.008), but the correlation was poor and negative in control fetuses (r = - 0.15; p = 0.001) (Figure 6). In a subgroup of fetuses with the lowest FBS pH (≤ 7.10), HF spectral powers of FHR variability correlated with FBS pH (r = 0.50; p = 0.018).

In summary, the HF spectral power of FHRV decreased with decreasing concomitant scalp pH-values. This indicates that there is decreased vagal activity in fetuses with marked intrapartum hypoxia.

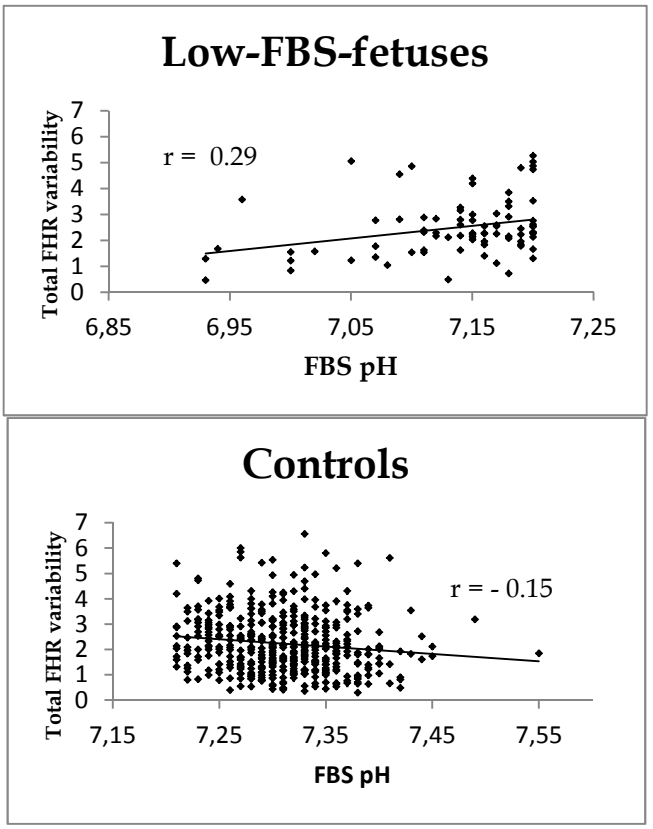

Figure 6. Correlation between total spectral power of FHRV and the FBS pH-values. The spectral power of FHRV is presented in arbitrary units (AU). (Study IV)

5.4 FHRV in relation to ST events (Study III)

A relative change greater than 30 % (increase or decrease) in the LF/HF ratio of FHRV in association with a ST event was associated with fetal metabolic acidosis (cord artery pH ≤ 7.05 and BD ≥ 12 mmol/l) (Figure 7). A change of this magnitude predicted fetal metabolic acidosis with a sensitivity of 89 % (95 % Cl 68–100 %) and specificity of 80 % (95 % Cl 64–96 %). Out one out of nine fetuses with metabolic acidosis was not identified with this cut-off value. Five fetuses who did not have metabolic acidosis had a change of more than 30 % in the LF/HF ratio, but three did have signs of oxygen deficiency - the cord artery pH was ≤ 7.05 and the BD > 8 mmol/l (Figure 8).

In summary, if the LF/HF changed markedly during delivery, 85 % of the fetuses had a cord pH ≤ 7.05.

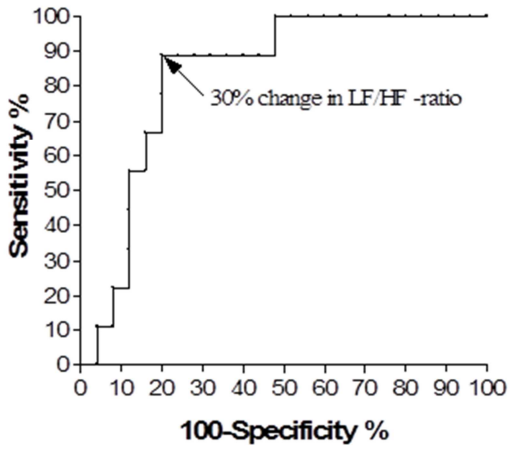

Figure 7. ROC curve of the relative change in the LF/HF -ratio of FHRV in relation to a significant ST event for predicting metabolic acidemia in arterial umbilical cord blood samples. (Study III)

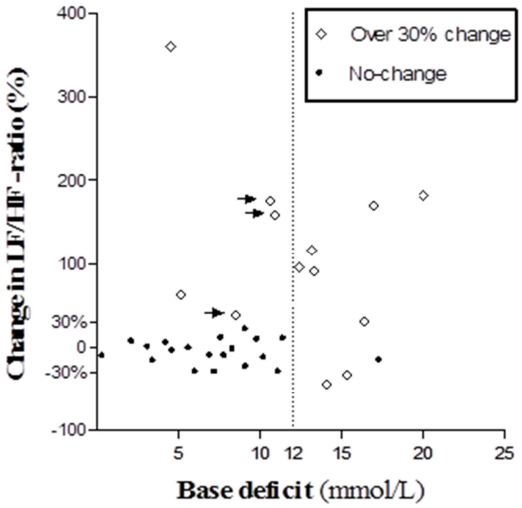

Figure 8. Relative change in spectral powers of the LF/HF ratio of FHRV associated with a significant ST event vs. cord arterial BD values in 34 fetuses. Cases marked with an arrow represent a fetus with pH ≤ 7.05, but BD 8- 12 mmol/l at birth. (Study III)

6. DISCUSSION

Accurate detection of intrapartum fetal acidosis is crucial for the prevention of neonatal morbidity, especially cerebral damage. Unnecessary operative interventions should be avoided to prevent maternal morbidity and complications in future pregnancies. Making clinical decisions adequately is challenging when based on interpretation of the CTG alone, but this is a drawback of STAN® method, as well. The driving concept of the studies in this thesis was to examine if spectral analysis of FHRV could provide objective information on fetal responses to oxygen deficiency by measuring hypoxia-related autonomic nervous system activation. Based on the results in our preliminary study (Study I), we proceeded to examine the value of spectral analysis in larger series of human fetuses, aiming to test whether intrapartum hypoxia can be detected with power spectral analysis of FHRV.

6.1 FHRV and intrapartum hypoxia

There appeared to be a large intraindividual variation in spectral powers of FHRV, and thus a single measure is not sufficient for determining fetal wellbeing. If the FHRV varies largely, this identifies a fetus capable of responding actively to the stress of labor and delivery, even if acidemia ensues. We found that during delivery, a marked (> 30 %) change in the LF/HF ratio of FHRV at the time of a significant ST event was associated with fetal metabolic acidosis (pH ≤ 7.05 and BD > 12.0 mmol/l), or a low cord arterial pH-value (≤ 7.05) at birth. These results are in line with experimental studies showing that progressive metabolic acidosis following repeated umbilical cord occlusions leads to an increase in FHRV, although FHRV may also decrease with progressing acidemia *(Westgate et al. 1999a)*. Clearly, changes in the FHRV are an important variable to be followed.

When studying the association of spectral powers with concomitant intrapartum hypoxia estimated by scalp FBS pH, we found that a healthy fetus responds to hypoxia by increasing its FHRV. In contrast, when the compensatory reserves of a fetus have been consumed, FHRV decreases due to deeper acidosis. Increased vagal activity may be critical for fetal outcome *(Frasch et al. 2009, Groome et al. 1999)*, and a lack of vagal activation compromises chemoreceptor-mediated fetal circulatory centralization during hypoxia *(Jensen et al. 1999)*. LF and especially HF spectral powers of FHRV correlate with vagal activity *(Groome et al. 1999)*. Our finding, that fetuses with the lowest intrapartum pH (FBS ≤ 7.10) had smaller HF FHRV compared with fetuses with higher FBS pH (7.11- 7.20) is in line with this hypothesis, as fetuses with the lowest FBS may already have consumed their compensating reserves. Thus, if the HF spectral power decreases, this may be due to an attenuation of the cardiovascular defense of the fetus.

6.2 FHRV and acidosis at birth

In fetuses acidotic at birth, all spectral powers of FHRV increased initially, but then gradually dropped as labor progressed. This finding agrees with previous human and experimental studies. In human fetuses, hypoxia increases the FHRV *(Kwon et al. 2011, Salamalekis et al. 2006)*, whereas in experimental studies marked acidosis decreases the FHRV *(Ikeda et al. 1998, Dalton et al. 1977)*. The decrease in spectral powers of FHRV in acidotic fetuses may represent a sign of fetal decompensation due to progressive hypoxic stress.

6.3 FHRV and non-hypoxic ST changes

It is known that ST changes in the fetal ECG may be due to other conditions than hypoxia, e.g. prematurity, infection, maternal fever, fetal myocardial dystrophy, cardiac malformations, and fetal stress hormone surges due to contractions during labor *(Amer-Wåhlin et al. 2011)*. During a normal, reactive CTG, these changes are thought to appear as a consequence of arousal reactions indicating that a fetus is responding to the strain of labor with surges of stress hormones *(Amer-Wåhlin et al. 2011)*. Nevertheless, clinicians can be confused in front of the STAN® alarms generated by such conditions, and it would be most useful if harmless ST changes could be distinguished from the ones caused by hypoxia. Based on our results, spectral analysis of FHRV may help to differentiate non-hypoxic ST changes from hypoxic ST changes, since a marked change in the relative spectral powers was associated with fetal metabolic acidosis (Study III, Fig. 8.). This finding needs to be corroborated in a larger study sample of fetuses with arousal reactions and, in larger group of fetuses with a poor outcome.

6.4 Methodological considerations

When fetal wellbeing during delivery is monitored with the STAN® method, the R-R interval data are freely available for analysis and spectral calculations. Thus, with slight equipment modifications, intrapartum FHRV data could be easily and continuously obtained simultaneously with fetal ECG, and any possible changes in FHRV spectral powers could be promptly analyzed. For future research, agreement on spectral bands is necessary in order to get comparable results.

Spectral analysis of FHRV requires a stationary signal, and for calculation of LF variability, a continuous signal segment of at least 75 seconds is needed *(Berntson et al. 1997)*. This is a shortcoming inherent to spectral analysis of FHRV, because during delivery, the FHR data is often non-stationary - there are signal breaks and large fluctuations caused by uterine and fetal activity. Therefore, we have studied the FHRV in short, two-minute signal segments. If there were large signal breaks in the two-minute R-R data segments, a new segment was started immediately after a break to minimize loss of data. Despite these procedures, signal segments were lost in 43-67% of study periods (Studies II-IV).

Because the FHR and FHRV are also dependent on each other, all FHRV data were corrected for baseline heart rate in studies I-IV *(Hayano et al. 1990)*. Several additional factors, such as GA, fetal activity and sleep states, uterine contractions, and medication also affect FHRV *(Park et al. 2001, Divon et al. 1985, Zimmer et al. 1998, Reynolds 2010)*. Modulation of FHRV matures with advancing GA, and in near-term fetuses GA affects the spectral powers of FHRV *(van Laar et al. 2009)*. This was also found in Study II, where HF spectral power (corresponding to vagal activity) increased with advancing GA. However, there were no differences in GA between the study groups in any of the studies. The number of gestational weeks was used as a covariate in Study IV, when calculating the correlation between spectral powers and the FBS pH-value, but this did not affect the result.

During labor, fetal movements decrease and, when they do occur, they are generally associated with uterine contractions *(Natale et al. 1981, Wittmann et al. 1979)*. During acidosis, fetal movements decrease further *(Natale et al. 1981)*. Fetal movements may increase LF FHRV, but there have also been contradictory results *(Breborowicz et al. 1988, Zimmer et al. 1988)*. Fetal movements were not assessed in this study. However, to minimize the effect of occasional fetal movements on spectral powers, several signal segments from each study period were analyzed and median spectral values were calculated. As hypoxia increases LF FHRV, any increase in spectral powers due to fetal movements in the control group would have narrowed the difference between the study groups by increasing LF FHRV.

Contractions are unlikely to contribute to the present results, since they do not occur at a frequency that could interfere with the detection by spectral analysis, i.e. at least three times within a 2-minute signal segment.

Maternal analgesia during delivery may also affect FHRV *(Palmer et al. 1999, Capogna 2001)*. However, the incidence of these FHR changes is low (6-12%), and all changes have been transient and resolved within 30 minutes *(Palmer et al. 1999)*. Therefore, we decided not to analyze separately fetuses by maternal analgesia.

6.5 Strengths and limitations

We studied intrapartum hypoxia in a large series of human fetuses collected as a part of multicenter studies. Despite having strict criteria for fetal and neonatal acidosis in Studies II-IV (FBS pH $\leq$7.20, and even $\leq$7.10; cord arterial pH $\leq$ 7.05 and BD $\geq$12 mmol/l) we had many affected fetuses with intrapartum acidosis and/or metabolic acidosis at birth.

We analyzed FHRV in human fetuses from new viewpoints, and studied how a fetus adapts to normal labor and delivery, and what happens if the fetus has acidosis.

The number of studied fetuses was not very large in the preliminary study (Study I) and in Study III. Especially the number of fetuses with “false ST alarms” was small, and the result of Study III needs to be confirmed in future studies. Further, the time lag from recording of the FHRV segments to measurement of the acid-base values at birth was occasionally (in studies I and III) several hours, which is far too long. Situations during labor and delivery change, and if the time lag is long, the spectrum of FHRV

may be analyzed before a fetus is exposed to hypoxic condition. However, in study III, the median time lag to birth was 48 minutes, which is a reasonable time -interval.

The main weaknesses of the spectral studies are that neither have the spectral bands of FHRV been standardized nor have the methods been established. Thus, the results cannot straightforward be compared with other studies.

6.6 Clinical implications

Can spectral analysis of FHRV be used in clinical practice? Our studies show that interpretation of complex FHR patterns can be aided by quantifying FHRV. We have seen that changes in spectral powers of FHRV are more marked in hypoxic and acidotic fetuses than controls, and that these changes in spectral powers occur even before changes in the basal heart rate are detectable (Study I). Further, a relative change in the LF/HF ratio in association with a significant ST event in the fetal ECG predicts metabolic acidosis in majority of the cases; the LF/HF ratio could be useful for separating ST events related to hypoxia from ST events due to physiological arousal reactions. This additional information on fetal well-being may help to prevent unnecessary operational deliveries. The range of normal spectral powers of FHRV is, however, wide and depends on the individual maturational state and physiological reserves of the fetus. Thus, spectral powers of FHRV should be analyzed longitudinally, and momentary spectral powers should be completed with those obtained earlier during labor (trend analysis).

6.7 Future research

Power spectral analysis is an interesting method for analyzing FHRV objectively during labor and delivery. Since the data in the present study is rather limited, larger observational studies are necessary. These studies were made off-line, and now on-line studies are needed to determine the clinical usefulness of spectral analysis in detecting fetal intrapartum hypoxia and acidosis. The challenge of on-line studies will be signal loss, but when short signal segments during labor are studied continuously, information loss is minimized.

Some interesting research question arise: Can spectral analysis of FHRV be used to differentiate non-significant ST events from hypoxic ST events in STAN® recordings? Is there an association between spectral powers and the amount of ST changes? The answers to these questions are important and raise a need for randomized clinical studies.

The relation between spectral powers of FHRV and various CTG features, e.g. FHR decelerations, also need attention. The influence of maternal diseases, e.g. diabetes and hypertension, on fetal autonomic nervous control of FHRV is not known and power spectral analysis presents itself as a method that could be used to examine these important relations.

7. SUMMARY AND CONCLUSIONS

Intrapartum FHRV was studied in human fetuses with power spectral analysis. R-R interval data was recorded with a STAN® monitor and fetal data was collected as part of multicenter STAN® studies. Spectral powers of FHRV were compared between acidotic and control fetuses, and the associations between spectral powers, acid-base values of umbilical cord arterial blood and ST changes of the fetal ECG were studied.

1. During the course of labor, spectral powers of FHRV were increased in all fetuses, suggesting that changes in spectral powers reflect the effects of autonomic cardiac control in mature fetuses in response to the stress of labor. This increase was more pronounced in fetuses with intrapartum hypoxia. In fetuses that were acidotic at birth, all spectral powers of FHRV dropped near delivery.

2. The association between a spectrum of FHRV and concomitant pH-values in blood samples taken from the scalp of the fetus was poor, and the range of spectral powers was wide. Thus, a single measure cannot identify a fetus at risk of acidosis. The technique might be useful for longitudinal assessment of changes in spectral powers of FHRV with time during labor: longitudinal data could provide more information on the oxygen state of the fetus.

3. Low-to-high frequency spectral powers of FHRV changed markedly in relation to fetal ECG ST events in fetuses with metabolic acidosis at birth. This change in the relative LF/HF powers may help to differentiate hypoxic ST events from physiological arousal reactions.

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REFERENCES

"Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology", 1996, *Circulation,* vol. 93, pp. 1043-165.

Agrawal, S.K., Doucette, F., Gratton, R., Richardson, B. & Gagnon, R. 2003, "Intrapartum computerized fetal heart rate parameters and metabolic acidosis at birth", *Obstet Gynecol,* vol. 102, no. 4, pp. 731-738.

Akselrod, S., Gordon, D., Ubel, F.A., Shannon, D.C., Berger, A.C. & Cohen, R.J. 1981, "Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control", *Science,* vol. 213, pp. 220-22.

Alfirevic Z, , Devane D, & Gyte GML 2008, "Continuous cardiotocography (CTG) as a form of electronic fetal monitorng (EFM) for fetal assessment during labour (Review)", *Cochrane Database Syst. Rev.,* , no. 4.

Alfirevic, Z., Devane, D. & Gyte, G.M. 2006, "Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour", *Cochrane Database Syst Rev,* vol. 3.

Amer-Wåhlin, I., Bordahl, P., Eikeland, T., Hellsten, C., Norén, H., Sornes, T. & Rosén, K.G. 2002, "ST analysis of the fetal electrocardiogram during labor: Nordic observational multicenter study", *J Matern Fetal Neonatal Med,* vol. 12, no. 4, pp. 260-266.

Amer-Wåhlin, I., Arulkumaran, S., Hagberg, H., Maršál, K. & Visser, G.H. 2007, "Fetal electrocardiogram: ST waveform analysis in intrapartum surveillance", *BJOG : an international journal of obstetrics and gynaecology,* vol. 114, no. 10, pp. 1191-1193.

Amer-Wåhlin, I. & Maršál, K. 2011, "ST analysis of fetal electrocardiography in labor", *Seminars in fetal & neonatal medicine,* vol. 16, no. 1, pp. 29-35.

Andres, R.L., Saade, G., Gilstrap, L.C., Wilkins, I., Witlin, A., Zlatnik, F. & Hankins, G.V. 1999, "Association between umbilical blood gas parameters and neonatal morbidity and death in neonates with pathologic fetal acidemia", *American Journal of Obstetrics and Gynecology,* vol. 181, no. 4, pp. 867-871.

Assali, N.S., Brinkman, C.R.,3rd, Woods, J.R.,Jr., Dandavino, A. & Nuwayhid, B. 1977, "Development of neurohumoral control of fetal, neonatal, and adult cardiovascular functions", *Am J Obstet Gynecol,* vol. 129, pp. 748-59.

Bailey, R.E. 2009, "Intrapartum fetal monitoring", *American Family Physician,* vol. 80, no. 12, pp. 1388-1396.

Becker, J.H., Bax, L., Amer-Wahlin, I., Ojala, K., Vayssiere, C., Westerhuis, M.E., Mol, B.W., Visser, G.H., Marsal, K., Kwee, A. & Moons, K.G. 2012, "ST analysis of the fetal electrocardiogram in intrapartum fetal monitoring: a meta-analysis", *Obstetrics and gynecology,* vol. 119, no. 1, pp. 145-154.

Bennet, L. & Gunn, A.J. 2009, "The fetal heart rate response to hypoxia: insights from animal models", *Clinics in perinatology,* vol. 36, no. 3, pp. 655-672.

Berntson, G.G., Bigger, J.T.,Jr, Eckberg, D.L., Grossman, P., Kaufmann, P.G., Malik, M., Nagaraja, H.N., Porges, S.W., Saul, J.P., Stone, P.H. & van der Molen, M.W. 1997, "Heart

rate variability: origins, methods, and interpretive caveats", *Psychophysiology*, vol. 34, no. 6, pp. 623-648.

Blix, E., Sviggum, O., Koss, K.S. & Oian, P. 2003, "Inter-observer variation in assessment of 845 labour admission tests: comparison between midwives and obstetricians in the clinical setting and two experts", *Bjog*, vol. 110, no. 1, pp. 1-5.

Block, B.S., Schlafer, D.H., Wentworth, R.A., Kreitzer, L.A. & Nathanielsz, P.W. 1990, "Intrauterine asphyxia and the breakdown of physiologic circulatory compensation in fetal sheep", *Am J Obstet Gynecol*, vol. 162, pp. 1325-131.

Bobrow, C.S. & Soothill, P.W. 1999, "Causes and consequences of fetal acidosis", *Archives of disease in childhood.Fetal and neonatal edition*, vol. 80, no. 3, pp. F246-9.

Bocking, A.D. 2003, "Assessment of fetal heart rate and fetal movements in detecting oxygen deprivation in-utero", *European journal of obstetrics, gynecology, and reproductive biology*, vol. 110 Suppl 1, pp. S108-12.

Bocking, A.D., Gagnon, R., Milne, K.M. & White, S.E. 1988, "Behavioral activity during prolonged hypoxemia in fetal sheep", *Journal of applied physiology (Bethesda, Md.: 1985)*, vol. 65, no. 6, pp. 2420-2426.

Boylan, P. & Lewis, P.J. 1980, "Fetal breathing in labor", *Obstet Gynecol*, vol. 56, pp. 35-38.

Breborowicz, G., Moczko, J. & Gadzinowski, J. 1988, "Quantification of the fetal heart rate variability by spectral analysis in growth-retarded fetuses", *Gynecol Obstet Invest*, vol. 25, pp. 186-191.

Bretscher, J. & Saling, E. 1967, "pH values in the human fetus during labor", *American Journal of Obstetrics and Gynecology*, vol. 97, no. 7, pp. 906-911.

Capogna, G. 2001, "Effect of epidural analgesia on the fetal heart rate", *Eur J Obstet Gynecol Reprod Biol*, vol. 98, pp. 160-14.

Chatow, U., Davidson, S., Reichman, B.L. & Akselrod, S. 1995, "Development and maturation of the autonomic nervous system in premature and full-term infants using spectral analysis of heart rate fluctuations", *Pediatr Res*, vol. 37, pp. 294-302.

Chauhan, S.P., Klauser, C.K., Woodring, T.C., Sanderson, M., Magann, E.F. & Morrison, J.C. 2008, "Intrapartum nonreassuring fetal heart rate tracing and prediction of adverse outcomes: interobserver variability", *American Journal of Obstetrics and Gynecology*, vol. 199, no. 6, pp. 623.e1-623.e5.

Chung, D.Y., Sim, Y.B., Park, K.T., Yi, S.H., Shin, J.C. & Kim, S.P. 2001, "Spectral analysis of fetal heart rate variability as a predictor of intrapartum fetal distress", *Int J Gynaecol Obstet*, vol. 73, pp. 109-116.

Costa, A., Ayres-de-Campos, D., Costa, F., Santos, C. & Bernardes, J. 2009, "Prediction of neonatal acidemia by computer analysis of fetal heart rate and ST event signals", *American Journal of Obstetrics and Gynecology*, vol. 201, no. 5, pp. 464.e1-464.e6.

Dalton, K.J., Dawes, G.S. & Patrick, J.E. 1983, "The autonomic nervous system and fetal heart rate variability", *Am J Obstet Gynecol*, vol. 146, no. 483228314, pp. 456-62.

Dalton, K.J., Dawes, G.S. & Patrick, J.E. 1977, "Diurnal, respiratory, and other rhythms of fetal heart rate in lambs", *Am J Obstet Gynecol*, vol. 127, no. 477109232, pp. 414-24.

Dawes, G., Meir, Y.J. & Mandruzzato, G.P. 1994, "Computerized evaluation of fetal heart-rate patterns", *J Perinat Med*, vol. 22, no. 6, pp. 491-499.

Dawes, G.S., Lobb, M., Moulden, M., Redman, C.W. & Wheeler, T. 1992, "Antenatal cardiotocogram quality and interpretation using computers", *Br J Obstet Gynaecol*, vol. 99, no. 10, pp. 791-797.

Dawes, G.S., Visser, G.H., Goodman, J.D. & Levine, D.H. 1981, "Numerical analysis of the human fetal heart rate: modulation by breathing and movement", *Am J Obstet Gynecol*, vol. 140, no. 581229720, pp. 535-44.

de Haan, M., Wyatt, J.S., Roth, S., Vargha-Khadem, F., Gadian, D. & Mishkin, M. 2006, "Brain and cognitive-behavioural development after asphyxia at term birth", *Developmental science*, vol. 9, no. 4, pp. 350-358.

Devoe, L.D. 2011, "Fetal ECG analysis for intrapartum electronic fetal monitoring: a review", *Clinical obstetrics and gynecology*, vol. 54, no. 1, pp. 56-65.

Divon, M.Y., Muskat, Y., Platt, L.D. & Paldi, E. 1984, "Increased beat-to-beat variability during uterine contractions: a common association in uncomplicated labor", *Am J Obstet Gynecol*, vol. 149, no. 884277882, pp. 893-86.

Divon, M.Y., Zimmer, E.Z., Platt, L.D. & Paldi, E. 1985, "Human fetal breathing: associated changes in heart rate and beat-to- beat variability", *Am J Obstet Gynecol*, vol. 151, no. 385119448, pp. 403-46.

Ferrazzi, E., Pardi, G., Setti, P.L., Rodolfi, M., Civardi, S. & Cerutti, S. 1989, "Power spectral analysis of the heart rate of the human fetus at 26 and 36 weeks of gestation", *Clin Phys Physiol Meas*, vol. 10, pp. 57-60.

Field, D.R., Parer, J.T., Auslender, R., Baker, B.W., Ross, B.K. & Leicht, C.H. 1991, "Fetal heart rate variability and cerebral oxygen consumption in fetal sheep during asphyxia", *Eur J Obstet Gynecol Reprod Biol*, vol. 42, no. 292111925, pp. 145-53.

Fleischer, A., Schulman, H., Jagani, N., Mitchell, J. & Randolph, G. 1982, "The development of fetal acidosis in the presence of an abnormal fetal heart rate tracing. I. The average for gestational age fetus", *Am J Obstet Gynecol*, vol. 144, no. 182281514, pp. 55-60.

Frasch, M.G., Muller, T., Weiss, C., Schwab, K., Schubert, H. & Schwab, M. 2009, "Heart rate variability analysis allows early asphyxia detection in ovine fetus", *Reproductive sciences (Thousand Oaks, Calif.)*, vol. 16, no. 5, pp. 509-517.

Gardner, D.S., Fowden, A.L. & Giussani, D.A. 2002, "Adverse intrauterine conditions diminish the fetal defense against acute hypoxia by increasing nitric oxide activity", *Circulation*, vol. 106, no. 17, pp. 2278-2283.

Gilbert, W.M., Jacoby, B.N., Xing, G., Danielsen, B. & Smith, L.H. 2010, "Adverse obstetric events are associated with significant risk of cerebral palsy", *American Journal of Obstetrics and Gynecology*, vol. 203, no. 4, pp. 328.e1-328.e5.

Giussani, D.A., Spencer, J.A., Moore, P.J., Bennet, L. & Hanson, M.A. 1993, "Afferent and efferent components of the cardiovascular reflex responses to acute hypoxia in term fetal sheep", *The Journal of physiology*, vol. 461, pp. 431-449.

Goldaber, K.G., Gilstrap, L.C.,3rd, Leveno, K.J., Dax, J.S. & McIntire, D.D. 1991, "Pathologic fetal acidemia", *Obstet Gynecol*, vol. 78, no. 6, pp. 1103-1107.

Groome, L.J., Loizou, P.C., Holland, S.B., Smith, L.A. & Hoff, C. 1999, "High vagal tone is associated with more efficient regulation of homeostasis in low-risk human fetuses", *Developmental psychobiology*, vol. 35, no. 1, pp. 25-34.

Groome, L.J., Mooney, D.M., Bentz, L.S. & Singh, K.P. 1994, "Spectral analysis of heart rate variability during quiet sleep in normal human fetuses between 36 and 40 weeks of gestation", *Early Hum Dev*, vol. 38, no. 195073404, pp. 1-9.

Hagberg, B., Hagberg, G. & Olow, I. 1993, "The changing panorama of cerebral palsy in Sweden. VI. Prevalence and origin during the birth year period 1983-1986", *Acta Paediatr*, vol. 82, no. 493306072, pp. 387-93.

Hayano, J., Sakakibara, Y., Yamada, M., Kamiya, T., Fujinami, T., Yokoyama, K., Watanabe, Y. & Takata, K. 1990, "Diurnal variations in vagal and sympathetic cardiac control", *Am J Physiol*, vol. 258, no. 3, pp. H642-6.

Heazell, A.E., Riches, J., Hopkins, L. & Myers, J.E. 2011, "Fetal blood sampling in early labour: is there an increased risk of operative delivery and fetal morbidity?", *BJOG : an international journal of obstetrics and gynaecology*, vol. 118, no. 7, pp. 849-855.

Heinis, A.M., Spaanderman, M.E., Gunnewiek, J.M. & Lotgering, F.K. 2011, "Scalp blood lactate for intra-partum assessment of fetal metabolic acidosis", *Acta Obstetricia et Gynecologica Scandinavica*, vol. 90, no. 10, pp. 1107-1114.

Himmelmann, K., Hagberg, G. & Uvebrant, P. 2010, "The changing panorama of cerebral palsy in Sweden. X. Prevalence and origin in the birth-year period 1999-2002", *Acta Paediatrica (Oslo, Norway : 1992)*, vol. 99, no. 9, pp. 1337-1343.

Hutter, D., Kingdom, J. & Jaeggi, E. 2010, "Causes and mechanisms of intrauterine hypoxia and its impact on the fetal cardiovascular system: a review", *International journal of pediatrics*, vol. 2010, pp. 401323.

Ikeda, T., Murata, Y., Quilligan, E.J., Parer, J.T., Theunissen, I.M., Cifuentes, P., Doi, S. & Park, S.D. 1998, "Fetal heart rate patterns in postasphyxiated fetal lambs with brain damage", *American Journal of Obstetrics and Gynecology*, vol. 179, no. 5, pp. 1329-1337.

Jensen, A., Garnier, Y. & Berger, R. 1999, "Dynamics of fetal circulatory responses to hypoxia and asphyxia", *Eur J Obstet Gynecol Reprod Biol*, vol. 84, no. 299355293, pp. 155-72.

Jones, C.T. & Robinson, R.O. 1975, "Plasma catecholamines in foetal and adult sheep", *The Journal of physiology*, vol. 248, no. 1, pp. 15-33.

Jonsson, M., Norden-Lindeberg, S., Ostlund, I. & Hanson, U. 2008, "Acidemia at birth, related to obstetric characteristics and to oxytocin use, during the last two hours of labor", *Acta Obstetricia et Gynecologica Scandinavica*, vol. 87, no. 7, pp. 745-750.

Kaita, T.M., Nikkola, E.M., Rantala, M.I., Ekblad, U.U. & Salonen, M.A. 2000, "Fetal oxygen saturation during epidural and paracervical analgesia", *Acta Obstet Gynecol Scand*, vol. 79, no. 520289604, pp. 336-40.

King, T. & Parer, J. 2000, "The physiology of fetal heart rate patterns and perinatal asphyxia", *The Journal of perinatal & neonatal nursing*, vol. 14, no. 3, pp. 19-39; quiz 102-3.

Koos, B.J., Kitanaka, T., Matsuda, K., Gilbert, R.D. & Longo, L.D. 1988, "Fetal breathing adaptation to prolonged hypoxaemia in sheep", *Journal of developmental physiology*, vol. 10, no. 2, pp. 161-166.

Kozuma, S., Watanabe, T., Bennet, L., Green, L.R. & Hanson, M.A. 1997, "The effect of carotid sinus denervation on fetal heart rate variation in normoxia, hypoxia and post-hypoxia in fetal sheep", *British journal of obstetrics and gynaecology*, vol. 104, no. 4, pp. 460-465.

Kruger, K., Hallberg, B., Blennow, M., Kublickas, M. & Westgren, M. 1999, "Predictive value of fetal scalp blood lactate concentration and pH as markers of neurologic disability", *Am J Obstet Gynecol*, vol. 181, no. 5, pp. 1072-1078.

Kwon, J.Y., Park, I.Y., Shin, J.C., Song, J., Tafreshi, R. & Lim, J. 2011, "Specific change in spectral power of fetal heart rate variability related to fetal acidemia during labor: Comparison between preterm and term fetuses", *Early human development*, .

Lange, S., Van Leeuwen, P., Geue, D., Hatzmann, W. & Gronemeyer, D. 2005, "Influence of gestational age, heart rate, gender and time of day on fetal heart rate variability", *Medical & biological engineering & computing*, vol. 43, no. 4, pp. 481-486.

Li, X., Tang, D., Zhou, S., Zhou, G., Wang, C., Zhuang, Y., Wu, G. & Shen, L. 2004, "Redistribution of power spectrum of heart rate variability during acute umbilical artery embolism and hypoxemia in late-gestation fetal sheep", *Eur J Obstet Gynecol Reprod Biol*, vol. 114, no. 2, pp. 137-143.

Lie, K.K., Groholt, E.K. & Eskild, A. 2010, "Association of cerebral palsy with Apgar score in low and normal birthweight infants: population based cohort study", *BMJ (Clinical research ed.)*, vol. 341, pp. c4990.

Low, J.A. 1997, "Intrapartum fetal asphyxia: definition, diagnosis, and classification", *Am J Obstet Gynecol*, vol. 176, no. 5, pp. 957-959.

Low, J.A., Lindsay, B.G. & Derrick, E.J. 1997, "Threshold of metabolic acidosis associated with newborn complications", *Am J Obstet Gynecol*, vol. 177, no. 698084356, pp. 1391-134.

Low, J.A., Panagiotopoulos, C. & Derrick, E.J. 1994, "Newborn complications after intrapartum asphyxia with metabolic acidosis in the term fetus", *Am J Obstet Gynecol*, vol. 170, no. 4, pp. 1081-1087.

Luttkus, A.K., Norén, H., Stupin, J.H., Blad, S., Arulkumaran, S., Erkkola, R., Hagberg, H., Lenstrup, C., Visser, G.H., Tamazian, O., Yli, B., Rosén, K.G. & Dudenhausen, J.W. 2004, "Fetal scalp pH and ST analysis of the fetal ECG as an adjunct to CTG. A multi-center, observational study", *J Perinat Med*, vol. 32, no. 6, pp. 486-494.

Mahendru, A.A. & Lees, C.C. 2011, "Is intrapartum fetal blood sampling a gold standard diagnostic tool for fetal distress?", *European journal of obstetrics, gynecology, and reproductive biology*, vol. 156, no. 2, pp. 137-139.

Malliani, A., Lombardi, F. & Pagani, M. 1994a, "Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms", *Br Heart J*, vol. 71, no. 194128476, pp. 1-2.

Malliani, A., Pagani, M. & Lombardi, F. 1994b, "Physiology and clinical implications of variability of cardiovascular parameters with focus on heart rate and blood pressure", *The American Journal of Cardiology*, vol. 73, no. 10, pp. 3C-9C.

Martin, C.B.,Jr 2008, "Normal fetal physiology and behavior, and adaptive responses with hypoxemia", *Seminars in perinatology*, vol. 32, no. 4, pp. 239-242.

Min, S.W., Ko, H. & Kim, C.S. 2002, "Power spectral analysis of heart rate variability during acute hypoxia in fetal lambs", *Acta Obstet Gynecol Scand*, vol. 81, no. 1122308599, pp. 1001-105.

Murotsuki, J., Bocking, A.D. & Gagnon, R. 1997, "Fetal heart rate patterns in growth-restricted fetal sheep induced by chronic fetal placental embolization", *American Journal of Obstetrics and Gynecology*, vol. 176, no. 2, pp. 282-290.

Natale, R., Clewlow, F. & Dawes, G.S. 1981, "Measurement of fetal forelimb movements in the lamb in utero", *Am J Obstet Gynecol*, vol. 140, no. 581229721, pp. 545-51.

Neilson, J.P. 2012, "Fetal electrocardiogram (ECG) for fetal monitoring during labour", *Cochrane database of systematic reviews (Online)*, vol. 4, pp. CD000116.

Neilson, J.P. 2006, "Fetal electrocardiogram (ECG) for fetal monitoring during labour", *Cochrane Database Syst Rev*, vol. 3, pp. CD000116.

NICE Clinical Guideline 2007 "Intrapartum care. Care of healthy women and their babies during childbirth.", .

Nordström, L. 2004, "Fetal scalp and cord blood lactate", *Best practice & research.Clinical obstetrics & gynaecology*, vol. 18, no. 3, pp. 467-476.

Norén, H., Amer-Wåhlin, I., Hagberg, H., Herbst, A., Kjellmer, I., Maršál, K., Olofsson, P. & Rosén, K.G. 2003, "Fetal electrocardiography in labor and neonatal outcome: data from the Swedish randomized controlled trial on intrapartum fetal monitoring", *Am J Obstet Gynecol*, vol. 188, no. 1, pp. 183-192.

Nuwayhid, B., Brinkman, C.R., Su, C., Bevan, J.A. & Assali, N.S. 1975, "Development of autonomic control of fetal circulation", *Am J Physiol*, vol. 228, pp. 337-344.

Oppenheimer, L.W. & Lewinsky, R.M. 1994, "Power spectral analysis of fetal heart rate", *Baillieres Clin Obstet Gynaecol*, vol. 8, no. 395112477, pp. 643-61.

Palmer, C.M., Maciulla, J.E., Cork, R.C., Nogami, W.M., Gossler, K. & Alves, D. 1999, "The incidence of fetal heart rate changes after intrathecal fentanyl labor analgesia", *Anesth Analg*, vol. 88, no. 399170225, pp. 577-81.

Parer, J.T. 1998, "Effects of fetal asphyxia on brain cell structure and function: limits of tolerance", *Comp Biochem Physiol A Mol Integr Physiol*, vol. 119, no. 398345653, pp. 711-76.

Parer, J.T. 1980, "The current role of intrapartum fetal blood sampling", *Clin Obstet Gynecol*, vol. 23, no. 280244869, pp. 565-82.

Parer, J.T. & Hamilton, E.F. 2010, "Comparison of 5 experts and computer analysis in rule-based fetal heart rate interpretation", *American Journal of Obstetrics and Gynecology*, vol. 203, no. 5, pp. 451.e1-451.e7.

Parer, J.T., King, T., Flanders, S., Fox, M. & Kilpatrick, S.J. 2006, "Fetal acidemia and electronic fetal heart rate patterns: is there evidence of an association?", *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, vol. 19, no. 5, pp. 289-294.

Park, M.I., Hwang, J.H., Cha, K.J., Park, Y.S. & Koh, S.K. 2001, "Computerized analysis of fetal heart rate parameters by gestational age", *Int J Gynaecol Obstet*, vol. 74, no. 221394017, pp. 157-64.

Peeters, L.L., Sheldon, R.E., Jones, M.D.,Jr., Makowski, E.L. & Meschia, G. 1979, "Blood flow to fetal organs as a function of arterial oxygen content", *Am J Obstet Gynecol,* vol. 135, no. 5, pp. 637-646.

Pello, L.C., Rosevear, S.K., Dawes, G.S., Moulden, M. & Redman, C.W. 1991, "Computerized fetal heart rate analysis in labor", *Obstet Gynecol,* vol. 78, no. 4, pp. 602-610.

Pierrat, V., Haouari, N., Liska, A., Thomas, D., Subtil, D., Truffert, P. & Groupe d'Etudes en Epidemiologie Perinatale 2005, "Prevalence, causes, and outcome at 2 years of age of newborn encephalopathy: population based study", *Archives of disease in childhood.Fetal and neonatal edition,* vol. 90, no. 3, pp. F257-61.

Pschirrer, E.R. & Yeomans, E.R. 2000, "Does asphyxia cause cerebral palsy?", *Semin Perinatol,* vol. 24, no. 320362909, pp. 215-20.

Pulgar, V.M., Hong, J.K., Jessup, J.A., Massmann, A.G., Diz, D.I. & Figueroa, J.P. 2009, "Mild chronic hypoxemia modifies expression of brain stem angiotensin peptide receptors and reflex responses in fetal sheep", *American journal of physiology.Regulatory, integrative and comparative physiology,* vol. 297, no. 2, pp. R446-52.

Renou, P., Newman, W. & Wood, C. 1969, "Autonomic control of fetal heart rate", *Am J Obstet Gynecol,* vol. 105, no. 670027816, pp. 949-53.

Reynolds, F. 2011, "Labour analgesia and the baby: good news is no news", *International journal of obstetric anesthesia,* vol. 20, no. 1, pp. 38-50.

Reynolds, F. 2010, "The effects of maternal labour analgesia on the fetus", *Best practice & research.Clinical obstetrics & gynaecology,* vol. 24, no. 3, pp. 289-302.

Ribbert, L.S., Fidler, V. & Visser, G.H. 1991a, "Computer-assisted analysis of normal second trimester fetal heart rate patterns", *Journal of perinatal medicine,* vol. 19, no. 1-2, pp. 53-59.

Ribbert, L.S., Snijders, R.J., Nicolaides, K.H. & Visser, G.H. 1991b, "Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses", *Br J Obstet Gynaecol,* vol. 98, no. 892001801, pp. 820-83.

Romano, M., Bifulco, P., Cesarelli, M., Sansone, M. & Bracale, M. 2006, "Foetal heart rate power spectrum response to uterine contraction", *Medical & biological engineering & computing,* vol. 44, no. 3, pp. 188-201.

Rosén, K.G., Dagbjartsson, A., Henriksson, B.A., Lagercrantz, H. & Kjellmer, I. 1984, "The relationship between circulating catecholamines and ST waveform in the fetal lamb electrocardiogram during hypoxia", *Am J Obstet Gynecol,* vol. 149, no. 284200355, pp. 190-15.

Rosén, K.G. & Lindecrantz, K. 1989, "STAN--the Gothenburg model for fetal surveillance during labour by ST analysis of the fetal electrocardiogram", *Clin Phys Physiol Meas,* vol. 10 Suppl B, pp. 51-56.

Sabir, H., Stannigel, H., Schwarz, A. & Hoehn, T. 2010, "Perinatal hemorrhagic shock after fetal scalp blood sampling", *Obstetrics and gynecology,* vol. 115, no. 2 Pt 2, pp. 419-420.

Sadovsky, E., Rabinowitz, R., Freeman, A. & Yarkoni, S. 1984, "The relationship between fetal heart rate accelerations, fetal movements, and uterine contractions", *Am J Obstet Gynecol,* vol. 149, no. 284200354, pp. 187-19.

Salamalekis, E., Hintipas, E., Salloum, I., Vasios, G., Loghis, C., Vitoratos, N., Chrelias, C. & Creatsas, G. 2006, "Computerized analysis of fetal heart rate variability using the matching pursuit technique as an indicator of fetal hypoxia during labor", *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, vol. 19, no. 3, pp. 165-169.

Salihagic-Kadic, A., Medic, M., Jugovic, D., Kos, M., Latin, V., Kusan Jukic, M. & Arbeille, P. 2006, "Fetal cerebrovascular response to chronic hypoxia--implications for the prevention of brain damage", *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, vol. 19, no. 7, pp. 387-396.

Schaap, T.P., Moormann, K.A., Becker, J.H., Westerhuis, M.E., Evers, A., Brouwers, H.A., Schuitemaker, N.W., Visser, G.H. & Kwee, A. 2011, "Cerebrospinal fluid leakage, an uncommon complication of fetal blood sampling: a case report and review of the literature", *Obstetrical & gynecological survey*, vol. 66, no. 1, pp. 42-46.

Schiermeier, S., Pildner von Steinburg, S., Thieme, A., Reinhard, J., Daumer, M., Scholz, M., Hatzmann, W. & Schneider, K.T. 2008, "Sensitivity and specificity of intrapartum computerised FIGO criteria for cardiotocography and fetal scalp pH during labour: multicentre, observational study", *BJOG : an international journal of obstetrics and gynaecology*, vol. 115, no. 12, pp. 1557-1563.

Sibony, O., Fouillot, J.P., Benaoudia, M., Benhalla, A., Oury, J.F., Sureau, C. & Blot, P. 1994, "Quantification of the fetal heart rate variability by spectral analysis of fetal well-being and fetal distress", *Eur J Obstet Gynecol Reprod Biol*, vol. 54, no. 294350130, pp. 103-18.

Siimes, A.S., Välimäki, I.A., Antila, K.J., Julkunen, M.K., Metsälä, T.H., Halkola, L.T. & Sarajas, H.S. 1990, "Regulation of heart rate variation by the autonomic nervous system in neonatal lambs", *Pediatr Res*, vol. 27, no. 4, pp. 383-91.

Spencer, J.A. 1993, "Clinical overview of cardiotocography", *Br J Obstet Gynaecol*, vol. 100 Suppl 993229436, pp. 4-7.

Thacker, S.B., Stroup, D. & Chang, M. 2003, "Continuous electronic heart rate monitoring for fetal assessment during labor", *The Cochrane Library*, , no. 4, pp. CD000063.

Thakor, A.S. & Giussani, D.A. 2009, "Effects of acute acidemia on the fetal cardiovascular defense to acute hypoxemia", *American journal of physiology.Regulatory, integrative and comparative physiology*, vol. 296, no. 1, pp. R90-9.

Välimäki, I. & Rantonen, T. 1999, "Spectral analysis of heart rate and blood pressure variability", *Clin Perinatol*, vol. 26, no. 4, pp. 967-80, x.

van Laar, J.O., Peters, C.H., Vullings, R., Houterman, S., Bergmans, J.W. & Oei, S.G. 2010, "Fetal autonomic response to severe acidaemia during labour", *BJOG : an international journal of obstetrics and gynaecology*, vol. 117, no. 4, pp. 429-437.

van Laar, J.O., Peters, C.H., Vullings, R., Houterman, S. & Oei, S.G. 2009, "Power spectrum analysis of fetal heart rate variability at near term and post term gestation during active sleep and quiet sleep", *Early human development*, vol. 85, no. 12, pp. 795-798.

Van Leeuwen, P., Geue, D., Lange, S., Hatzmann, W. & Gronemeyer, D. 2003, "Changes in the frequency power spectrum of fetal heart rate in the course of pregnancy", *Prenat Diagn,* vol. 23, no. 11, pp. 909-916.

van Ravenswaaij-Arts, C.M., Kollee, L.A., Hopman, J.C., Stoelinga, G.B. & van Geijn, H.P. 1993, "Heart rate variability", *Ann Intern Med,* vol. 118, no. 693175795, pp. 436-47.

Verklan, M.T. & Padhye, N.S. 2004, "Spectral analysis of heart rate variability: an emerging tool for assessing stability during transition to extrauterine life", *Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG,* vol. 33, no. 2, pp. 256-265.

Visser, G.H., Carse, E.A., Goodman, J.D. & Johnson, P. 1982, "A comparison of episodic heart-rate patterns in the fetus and newborn", *Br J Obstet Gynaecol,* vol. 89, no. 182135407, pp. 50-5.

Wakatsuki, A., Murata, Y., Ninomiya, Y., Masaoka, N., Tyner, J.G. & Kutty, K.K. 1992, "Autonomic nervous system regulation of baseline heart rate in the fetal lamb", *Am J Obstet Gynecol,* vol. 167, no. 292359199, pp. 519-23.

Walker, A.M., Cannata, J., Dowling, M.H., Ritchie, B. & Maloney, J.E. 1978, "Sympathetic and parasympathetic control of heart rate in unanaesthetized fetal and newborn lambs", *Biol Neonate,* vol. 33, no. 3-478236034, pp. 135-143.

Wassink, G., Bennet, L., Booth, L.C., Jensen, E.C., Wibbens, B., Dean, J.M. & Gunn, A.J. 2007, "The ontogeny of hemodynamic responses to prolonged umbilical cord occlusion in fetal sheep", *Journal of applied physiology (Bethesda, Md.: 1985),* vol. 103, no. 4, pp. 1311-1317.

Westgate, J.A., Bennet, L. & Gunn, A.J. 1999a, "Fetal heart rate variability changes during brief repeated umbilical cord occlusion in near term fetal sheep", *Br J Obstet Gynaecol,* vol. 106, no. 799355476, pp. 664-71.

Westgate, J.A., Gunn, A.J. & Gunn, T.R. 1999b, "Antecedents of neonatal encephalopathy with fetal acidaemia at term", *British journal of obstetrics and gynaecology,* vol. 106, no. 8, pp. 774-782.

Wheeler, T. & Murrills, A. 1978, "Patterns of fetal heart rate during normal pregnancy", *Br J Obstet Gynaecol,* vol. 85, no. 1, pp. 18-27.

Wiberg, N., Kallen, K. & Olofsson, P. 2006, "Base deficit estimation in umbilical cord blood is influenced by gestational age, choice of fetal fluid compartment, and algorithm for calculation", *American Journal of Obstetrics and Gynecology,* vol. 195, no. 6, pp. 1651-1656.

Widmark, C., Hökegård, K.H., Lagercrantz, H., Lilja, H. & Rosén, K.G. 1989, "Electrocardiographic waveform changes and catecholamine responses during acute hypoxia in the immature and mature fetal lamb", *Am J Obstet Gynecol,* vol. 160, no. 5, pp. 1245-1250.

Williams, K.P. & Galerneau, F. 2002, "Fetal heart rate parameters predictive of neonatal outcome in the presence of a prolonged deceleration", *Obstet Gynecol,* vol. 100, no. 5, pp. 951-94.

Wittmann, B.K., Davison, B.M., Lyons, E., Frohlich, J. & Towell, M.E. 1979, "Real-time ultrasound observation of fetal activity in labour", *Br J Obstet Gynaecol,* vol. 86, no. 479166225, pp. 278-81.

Yu, Z.Y., Lumbers, E.R., Gibson, K.J. & Stevens, A.D. 1998, "Effects on hypoxaemia on foetal heart rate, variability and cardiac rhythm", *Clin Exp Pharmacol Physiol*, vol. 25, no. 7-8, pp. 577-584.

Zimmer, E.Z., Divon, M.Y. & Vadasz, A. 1988, "Fetal heart rate beat-to-beat variability in uncomplicated labor", *Gynecol Obstet Invest*, vol. 25, no. 288226186, pp. 80-82.

Zimmer, E.Z., Divon, M.Y. & Vadasz, A. 1987, "The relationship between uterine contractions, fetal movements and fetal heart rate patterns in the active phase of labor", *Eur J Obstet Gynecol Reprod Biol*, vol. 25, no. 2, pp. 89-95.

Zimmer, E.Z., Paz, Y., Copel, J.A. & Weiner, Z. 1998, "The effect of uterine contractions on intrapartum fetal heart rate analyzed by a computerized system", *Am J Obstet Gynecol*, vol. 178, no. 398198911, pp. 436-40.

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Periodic spectral components of fetal heart rate variability reflect the changes in cord arterial base deficit values: a preliminary report

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Abstract

Fetal distress changes the function of the autonomic nervous system. These changes are reflected in the fetal heart rate and can be quantified with power spectrum analysis of heart rate variability. The purpose of this study was to find out whether spectral components of fetal heart rate variability (FHRV) during labor are associated with fetal cord arterial base deficit values at birth. The association between FHRV and umbilical cord arterial base deficit was studied in 14 singleton fetuses with normal pregnancy at 35–40 weeks of gestation. Fetal ECG was recorded by scalp-electrode using a STAN® Fetal ECG monitor (Cinventa Ab, Mölndal, Sweden). FHRV was quantified by computing Fast-Fourier-transformed heart rate (HR) spectra at three frequency bands: low-frequency (LF) 0.03–0.07 Hz, mid-frequency (MF) 0.07–0.13 Hz and high-frequency (HF) 0.13–1.0 Hz. We found that total FHRV and MF FHRV were lower in fetuses with cord arterial base deficit 8 to 12 mmol/L in comparison to the fetuses with normal cord arterial base deficit value ($P = 0.02$ and $P = 0.01$, respectively). A linear correlation was found between the spectral densities and the cord arterial base deficit values ($r = 0.4$ and $r = 0.6$, respectively). We conclude that the results suggest changes in the autonomic nervous cardiac control in fetuses with cord arterial base deficit between 8 to 12 mmol/L. The clinical applicability of our observations on FHRV in predicting fetal distress remains to be further studied.

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Keywords: Fetal heart rate variability; Fetal distress; Power spectrum analysis; Fetal metabolic acidosis

1. Introduction

The early accurate detection of fetal hypoxia during labor is of crucial importance. The sensitivity of non-invasive methods such as cardiotocography (CTG) used in assessing fetal well-being is often limited and the predictive value of an abnormal FHR pattern is low. Therefore, new tools are required to improve early diagnosis of fetal hypoxia. The degree of metabolic acidosis as measured from the umbilical arterial blood after birth reflects the cumulative hypoxic events that have occurred during the labor [1]. No general consensus has yet been reached on the definition of the threshold markers of decompensation. However, an umbilical artery base deficit of 12 mmol/L has been associated with moderate and severe neonatal asphyxic complications and a base deficit from 8 to 12 mmol/L are connected with minor complications in the newborn. The normal arterial base deficit values range from 4 to 8 mmol/L [2]. In experimental studies, the autonomic nervous system activation has been related to early induction of hypoxia [3], whereas depression has been associated to prolonged situation [4]. The balance of this autonomic nervous cardiac control can be quantitatively estimated by spectral analysis of heart rate variability [4]. We wanted to study whether spectral components of fetal heart rate variability (FHRV) during labor are associated with the values of cord arterial base deficit in human fetuses at birth.

2. Patients

Fourteen fetuses at 35–40 weeks of gestation after normal singleton pregnancy were examined. The babies were born on a median of 2 h (1–8 h) after a fetal ECG had been recorded and the arterial cord blood samples were obtained at delivery. The mothers did not receive any medication except intravenous oxytocin during the labor. Epidural analgesia was given to eleven mothers about 2 h before fetal ECG was recorded.

3. Methods

The fetal ECG was recorded for 15 min with an intrauterine scalp-electrode using a STAN® Fetal ECG monitor (Cinventa Ab, Mölndal, Sweden) and stored on a magnetic tape with an FM tape recorder (Store 4 DS, Racall Recorders, Southampton, UK). The fetal ECG was replayed and fed into a PC (Pentium 120 MHz) computer. The Dasylab (Data Acquisition System Laboratory)® program (Dosesoft, Tampere, Finland) was used for digitizing the fetal ECG signal. One 2 min noise-free signal segment was visually selected from each ECG. Visual selection was made by a ADP designer who was blinded to the grouping, clinical details and CTG of the fetuses. A

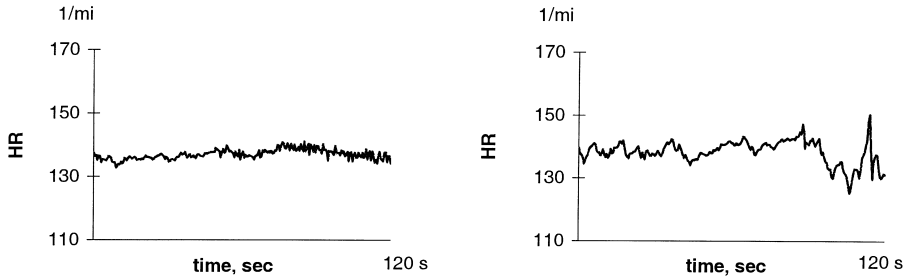

Fig. 1. Instantaneous heart rate patterns of a fetus with cord arterial base deficit above 8 mmol/L (left-hand panel) and another fetus with cord arterial base deficit value below 8 (right-hand panel).

voltage threshold trigger was used to detect each R wave and form an event-series of beat-to-beat intervals. The R–R intervals were measured at a sampling rate of 1 kHz, providing a time resolution of 1 ms. The reciprocal of each R–R interval sample was computed to obtain the respective instantaneous HR signal. After linear interpolation of consecutive heart beats, the events series was resampled at a rate of 16 Hz. To avoid aliasing, the signal was low-pass filtered and decimated by 8. The linear trend was removed from the HR signal. Fast-Fourier-transformed power spectra were then computed for the HR signal segments (MATLAB® oriented tailor-made signal analysis program, MARAPS, Tampere, Finland) (Fig. 1).

Spectral density of fetal HR variability was integrated over the frequency band of 0.03–1.0 Hz (1.8–60 cycles/min) and over three other frequency bands: low-frequency (LF) band from 0.03 to 0.07 Hz (1.8–4.2 cycles/min) as an indicator of mainly sympathetic activity [5], mid-frequency (MF) band from 0.07 to 0.13 Hz (1.8–7.8 cycles/min) indicating both sympathetic and parasympathetic nervous control [6] and high-frequency (HF) band from 0.13 Hz to 1.0 Hz (7.8–60 cycles/min) which mainly corresponds to parasympathetic nervous control [7]. All measurements of spectral densities are given in arbitrary units (AU).

Table 1
Clinical data of the study groups

Fetuses with	Base deficit below −8 mmol/L ($n = 8$)	Base deficit above −8 mmol/L ($n = 6$)
Pregnancy data		
Birth weight (g)	3107±465	3432±394
Gestational age (wk)	38±3	39±2
Placental index	0.17±0.02	0.16±0.03
1-min Apgar score	8±1	9±1
Cord arterial blood gas values		
Cord arterial pH	7.23±0.09	7.31±0.08
Cord arterial pCO_2	6.03±2.03	6.6±1.6
Cord arterial pO_2	3.8±1.6	3.3±1.0
Cord arteiral HCO3**	16.4±0.7	21.3±2.1

** $P < 0.005$.

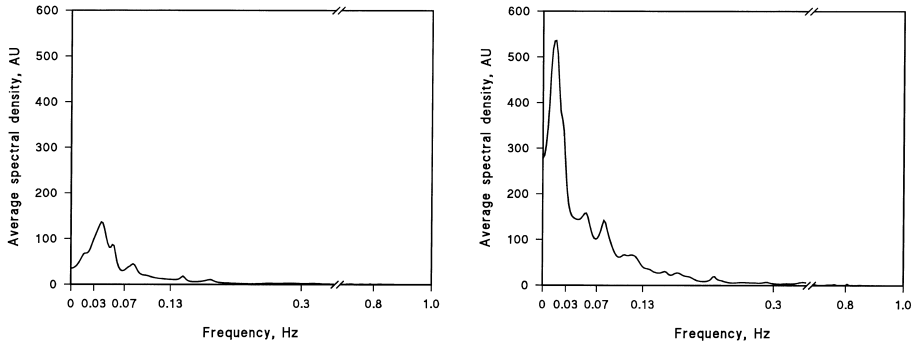

Fig. 2. The averaged FHRV spectral densities (±S.D.) of six fetuses with cord arterial base deficit values from 8 to 12 mmol/L (left-hand panel) and eight fetuses with normal cord arterial base deficit values (right-hand panel). The fetuses with higher cord arterial base deficit values had significant decrease in total (0.03–1. 0 Hz) and mid-frequency (0.07–0.13 Hz) fetal heart rate variability. (AU = arbitrary units).

4. Statistical analysis

The fetuses were divided into two groups according to the cord arterial base deficit value: (1) those with umbilical artery base deficit below 8 mmol/L and (2) those with the base deficit from 8 to 12 mmol/L. The Mann–Whitney *U*-test was used to compare the two groups. The correlation between the spectral band HRV densities and cord arterial base deficit values was estimated by Spearman correlation test.

5. Results

The fetuses with cord arterial base deficit from 8 to 12 mmol/L ($n = 6$) had decreased mean total spectral HRV (8.2±5.2 S.D. AU, vs. 27.1±17.7 S.D., $P = 0.01$) and MF spectral HRV (1.3±1.0 S.D. vs. 4.6±2.6 S.D., $P = 0.01$, Fig. 2) in comparison with the fetuses with normal base deficit values ($n = 8$). The decrease in HF or LF oscillations of FHRV did not quite reach statistical significance (1.5±1.0 S.D. vs. 4.1±3.5 S.D., $P = 0.05$ and 3.4±2.9 S.D. vs. 5.8±4.0, $P = 0.05$). A linear correlation between MF spectral HRV and cord arterial base deficit was found ($r = -0.6$, $P = 0.02$, respectively, tested with Spearman correlation test). There were no significant intergroup differences in the mean HR, birth weight, gestational age, fetal gender, placental index (the ratio of the placental weight to birth weight) or Apgar scores of the babies (Table 1). No abnormalities were found in the cardiotocographic recordings in studied fetuses (data not shown).

6. Discussion

We found that FHRV was decreased in the fetuses with slightly elevated cord arterial base deficit from 8 to 12 mmol/L in comparison to the fetuses with normal

base deficit values. The results suggest that autonomic cardiac control is changed and can be detected by spectral analysis of HRV in fetuses with risk for minor neonatal complications. These changes are apparent before any detectable changes in the mean HR can be noticed.

Acute short-term fetal hypoxia leads to increased FHRV in fetal lambs as shown by Parer et al. [8]. The ability of the cardiovascular control system to increase HRV in hypoxia is a sign of adequate fetal compensatory mechanisms. The cord arterial base deficit suggests that the fetus has been repeatedly under stress during labor [1]. Fetal metabolic acidemia, caused by long-term insufficiency in the placental gas exchange, leads to decreased HRV in fetal sheep [9]. As assessed by computation the difference between the longest and shortest R–R interval for every minute [9]. A decrease in spectral measures of HRV has been reported to indicate and predict the severity of the disease and injury in critically ill neonates [10–12]. Our results show that a decrease in the oscillations of the fetal heart rate during labor is associated with an unfavorable acid–base balance of the neonate. Interestingly, FHRV decreases in fetuses with cord arterial base deficit values from 8 to 12 mmol/L before any detectable changes in the mean HR. An equal cord arterial base deficit has previously been associated with minor complications in the cardiovascular and central nervous system in newborns. More severe increase in the cord arterial base deficit value appears to be connected to severe neonatal complications [2].

The gestational age and, consequently, maturation of the autonomic nervous system considerably affect the fetal hemodynamic responses to distress [13,14]. However, the gestational age was similar in both study groups. Further, external factors such as uterine activity and maternal medication affect the fetal heart rate [15,16]. However, in our subjects uterine contractions cannot cause periodic changes in fetal HR because of the short signal segments. Secondly, epidural analgesia (EA) has been reported to affect fetal HR. In this study heart rate of the fetuses whose mothers received EA during labor did not differ from the ones without EA. The analyzed FHR segment was rather short, because a stationary signal is required for spectral analysis and long segments often contain global or long-term trends.

In conclusion, we found that fetuses with cord arterial base deficit between 8 to 12 mmol/L have decreased FHRV as assessed by spectral analysis although the baseline heart rate remained unchanged. Thus, spectral analysis of FHRV may be a useful measure to find fetuses at risk of acidosis. The observed changes may rather originate from changed sympathetic than vagal activity, because vagal nervous system is still rather immature in fetuses [17]. The clinical usefulness of our observations on FHRV patterns in predicting fetal distress remains to be verified in further studies.

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References

[1] Low JA. The relationship of asphyxia in the mature fetus to long-term neurologic function. Clin Obstet Gynecol 1993;36:82–90.
[2] Low J, Lindsay BG, Derric EJ. Threshold of metabolic acidosis associated with newborn complications. Am J Obstet Gynecol 1997;177:1391–4.
[3] Sayers BMCA. Analysis of heart rate variability. Ergonomics 1973;16:17–32.
[4] Akselrod S, Goldon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuations: quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220–2.
[5] Pagani M, Montano N, Porta A, Malliani A, Abboud FM, Birkett C, Somers VK. Relationship between spectral components of cardiovascular variability and direct measures of muscle sympathetic nerve activity in humans. Circulation 1997;95:1441–8.
[6] Madwed JB, Albrecht P, Mark RG, Cohen RJ. Low-frequency oscillations in arterial pressure and heart rate: a simple computer model. Am J Physiol 1989;256:H1573–9.
[7] Randall DC, Brown DR, Raisch RM, Ylingling JD, Randall WC. SA nodal parasympathectomy delineates autonomic control of heart rate power spectrum. Am J Physiol 1991;248:H151–3.
[8] Parer J, Dijkstra H, Vredebregt P, Harris J, Krueger T, Reuss M. Increased fetal heart rate variability with acute hypoxia in chronically instrumented sheep. Eur J Obstet Gynaecol Reprod Biol 1980;10:393–9.
[9] Murotsuki J, Bocking A, Gagnon R. Fetal heart rate patterns in growth-restricted fetal sheep induced by chronic fetal placental embolization. Am J Obstet Gynecol 1997;176:282–90.
[10] Kero P, Antila K, Ylitalo V, Välimäki I. Decreased heart rate variability in decerebration syndrome: quantitation clinical criterion of brain death? Pediatrics 1978;62:307–11.
[11] Goldstein B, Fiser D, Kelly M, Mickelsen D, Ruttimann U, Pollack M. Decomplexification in critical illness and injury: relationship between heart rate variability, severity of illness, and outcome. Pediatr Crit Care 1998;26:352–7.
[12] Äärimaa T, Oja R. Transcutaneous pO2, pCo2 and neonatal heart rate patterns during normal postnatal adaptation and respiratory distress. Early Hum Dev 1988;16:3–11.
[13] Widmark C, Hökegård K-H, Lagercrantz H, Lilja H, Rosen KG. Electrocardiographic waveform changes and catecholamine responses during acute hypoxia in the immature and mature fetal lamb. Am J Obstet Gynecol 1989;160:1245–50.
[14] Karin J, Hirsch M, Akselrod S. An estimate of fetal autonomic state by spectral analysis of fetal heart rate fluctuations. Pediatr Res 1993;34:134–8.
[15] Zimmer EZ, Paz Y, Copel JA, Weiner Z. The effect of uterine contractions on intrapartum fetal heart rate analyzed by a computer system. Am J Obstet Gynecol 1998;178:436–40.
[16] Pello LC, Rosevear SK, Dawes GS, Moulden M, Redman CWG. Computerized fetal heart rate analysis of labor. Am J Obstet Gynecol 1991;78:602–10.
[17] Siimes AS, Välimäki IAT, Antila KJ, Julkunen MKA, Metsälä TH, Halkola LT, Sarajas SS. Regulation of heart rate variability by the autonomic nervous system in neonatal lambs. Pediatr Res 1990;27:383–91.

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Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour

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Objective To assess whether intrapartum acidosis affects specific components of fetal heart rate variability.

Design Prospective clinical study.

Setting Twelve Nordic delivery units.

Subjects Fetal heart rate variability was studied in 334 fetuses divided into two groups according to cord pH value: the acidotic group (cord arterial pH <7.05 at birth, $n = 15$) and the control group (cord arterial pH ≥ 7.05 at birth, $n = 319$).

Methods In spectral analysis of fetal heart rate variability, frequencies were integrated over the total frequency band (0.04–1.0 Hz), low-frequency band (0.04–0.15 Hz) and high-frequency band (0.15–1.0 Hz). We also calculated the low-to-high frequency ratio.

Main outcome measures The spectral bands of fetal heart rate variability were compared between the acidotic and control fetuses.

Results We found that during the last hour of monitoring, baseline fetal heart rate gradually decreased, whereas total, low-frequency and high-frequency fetal heart rate variability initially increased but then, near the delivery, decreased in the acidotic fetuses when compared with the controls. Low-to-high frequency ratio was greater in the acidotic group during the whole study period ($P = 0.002$). Cord artery pH was inversely associated with total fetal heart rate variability ($P < 0.001$), low-frequency fetal heart rate variability ($P < 0.001$) and low-to-high frequency ratio ($P = 0.004$).

Conclusions Marked fetal acidosis was associated with frequency-specific changes in fetal heart rate variability as reflecting the compensation ability of autonomic nervous activation during the last hour of labour.

INTRODUCTION

Early and accurate detection of fetal asphyxia is crucial to prevent fetal morbidity, especially cerebral damage. Cardiotocography is widely used to monitor fetal wellbeing during delivery. However, cardiotocography has several limitations: the positive predictive value of abnormal intrapartum fetal heart rate patterns for fetal acidaemia is only around 30%, and continuous cardiotocography monitoring may increase unnecessary operative interventions.[1] Also, visual interpretation of fetal heart rate traces is subjective. This may lead to high inter-observer variability, especially in tracings that are not reactive, and a kappa value as low as 0.33 has been reported. However, in normal tracings, the agreement between various analysts is better, the kappa value being 0.86.[2]

Automatic computerised analysis of the fetal heart rate pattern during labour may be a method to improve the accuracy and consistency of detecting specific fetal heart rate patterns. Computerised analysis of fetal heart rate variation has been successfully applied to fetal heart rate tracings obtained prior to the onset of labour.[3] The system is based on applying standard techniques of fetal heart rate beat-to-beat variance measurements and does not lend itself to continuous fetal heart rate variability assessments in a non-stationary fetal heart rate signal (a signal that shows linear or global trends). Unfortunately, computerised fetal heart rate variability has not proved helpful during labour.[4] However, modern signal processing techniques may be of value in providing further information on changes in fetal heart rate variation during labour.

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During the development of fetal hypoxia, the autonomic nervous system becomes activated and this causes changes in fetal heart rate control.[5] This is an important sign of adequate circulatory adaptation in a compromised fetus. Fetal heart rate oscillates at specific frequencies, because of the negative feedback and time-delay of the cardiovascular control system.[6] A frequency-specific assessment of fetal heart rate by power spectral analysis may be used to monitor non-invasively features of fetal autonomic cardiac control.[5,7,8] However, in acidotic human fetuses, the value of spectral analysis in detecting changes in cardiac control is still poorly known. The aim of the study was to test whether term fetuses born with marked cord artery acidaemia would display differences in fetal heart rate spectral analysis during the last hour of the recording compared with a non-acidotic control group.

METHODS

We analysed spectral band densities of fetal heart rate signal sets from the last hour of delivery in 356 live born fetuses. The recordings were collected from 12 Nordic delivery units from June 1998 to January 1999 as a part of a Nordic observational multicentre study.[9] Those eligible for the study were women in active labour at more than 35 completed gestational weeks, and for whom a clinical decision had been made to apply a fetal scalp electrode for continuous internal cardiotocography recording. The umbilical cord arterial acid–base status was analysed after delivery. None of the fetuses had major cardiac anomalies. We excluded 22 out of 356 (6%) fetuses because of the poor quality of the electrocardiogram (ECG). The ethics committees of the participating hospitals approved the study and all mothers gave their informed consent.

The fetuses were divided into two groups according to their cord arterial pH value at birth: (1) the acidotic group had a pH <7.05 ($n = 15$) and (2) the control group had a pH ≥ 7.05 ($n = 319$). The current database has been analysed in another study regarding ST waveform changes in fetal ECG.[9] All the acidotic fetuses displayed an increase in T/QRS ratio, with ST segment elevation on average 24 (median), 18–33 minutes (95th CI) before the end of recording. In the present study, the median time lag between the end of recording and delivery was 4 minutes, 1–9 minutes (95th CI) in acidotic fetuses, of whom all but one were delivered vaginally. There was no difference in proportion of excluded fetuses between study groups ($P = 0.09$). The clinical data of the fetuses are shown in Table 1.

The fetal ECG was recorded during delivery with an intrauterine scalp electrode using a STAN®S 21 monitor (Neoventa Medical, Gothenburg, Sweden). The fetal unipolar ECG lead configuration consisted of a single-helix scalp electrode and a maternal skin electrode. The R-peaks were detected and R–R intervals were measured and digitised at a sampling rate of 500 Hz. The R–R interval data sets were stored on a PC hard disk and the intervals from the last hour of delivery were analysed offline. Two-minute continuous signal segments of stationary fetal heart rate were required for spectral analysis. The quality of these segments was visually controlled by our signal analyst (J.J.) who was blinded to the grouping and clinical details of the fetuses. On average, 10 segments (range from 1 to 29) were obtained from each fetus. The mean time lag from the last studied R–R interval to the end of recording and the number of ECG segments studied were similar in both groups. However, due to the reduction in the number of 2-minute epoques of continuous fetal heart rate signal during the last 10 minutes of the recording, the last epoque analysed in the acidotic group was obtained 8 minutes before the end of recording.

The R–R interval data sets were transformed to a continuous digital signal by linear interpolation, and then the event series were resampled at the rate of 16 Hz. The reciprocal of each R–R interval was computed to obtain the respective instantaneous heart rate reading. Fast-Fourier-Transformed power spectra were then computed for the fetal heart rate signal segments (MATLAB®-oriented tailor-made signal analysis program, MARAPS, Tampere, Finland).[10]

Fetal heart rate variability spectrum was integrated over the total frequency band (0.04–1.0 Hz) as well as over the low-frequency band from 0.04 to 0.15 Hz (from 2.4 to 7.8 cycles/minute) corresponding mainly to sympathetic and parasympathetic control, and over the high-frequency

Table 1. Clinical data of 15 acidotic and 319 control fetuses. Values are expressed as mean (range) or median [range] unless stated otherwise. P = statistical significance for difference between the study groups.

	Acidotic fetuses	Control fetuses	P
Gestational age, weeks	40 [35 to 42]	40 [36 to 43]	0.89*
Birthweight, g	3339 (2050 to 4450)	3602 (1600 to 5630)	0.07†
No. of caesarean section (%)	1 (7)	38 (12)	1.00§
5-minute Apgar score	8 [3 to 10]	10 [5 to 10]	<0.001*
Cord arterial pH	6.93 (6.75 to 7.03)	7.22 (7.05 to 7.45)	<0.001†
Cord arterial base deficit, mmol/L	12.6 (7.9 to 18.0)	5.2 (−3.7 to 11.3)	<0.001†

* Wilcoxon two-sample test.
† Two-sample t test.
§ Fisher's exact test.

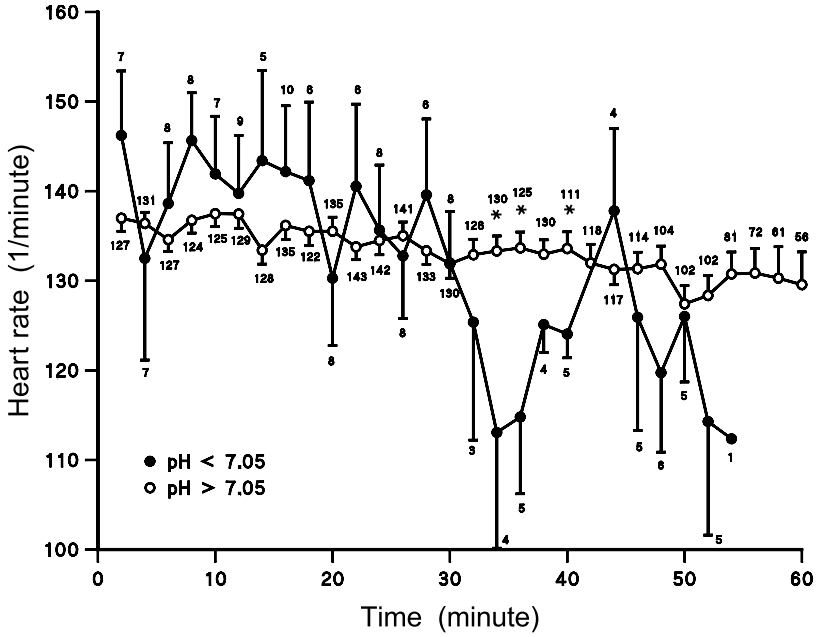

Fig. 1. Mean fetal heart rate during the last hour of labour in the acidotic fetuses (pH $<$ 7.05) and the control fetuses (pH $\geq$ 7.05). There was a significant interaction between the study groups and time of the study period ($P = 0.001$; ANOVA for repeated measures). Number of signal segment samples is presented above the measuring points. * = significant difference between groups ($P < 0.05$; two-sample t test).

band from 0.15 to 1.0 Hz (from 7.8 to 60 cycles/minute) corresponding to parasympathetic control.[11] Fetal heart rate may itself alter fetal heart rate variability. To minimise such an effect, we calculated the coefficient of component variance (square root of power spectra/mean R–R interval).[12] We also calculated the low-to-high frequency ratio to display the balance of sympathetic and parasympathetic control.[11] All the spectral variability data are given in arbitrary units (AU).

Longitudinal data of fetal heart rate and fetal heart rate variability parameters were analysed using analysis of variance (ANOVA) for repeated measures where grouping factor (acidotic or control) and within factor (time of study period) were independent variables. Because of the skewed distribution of data, the fetal heart rate variability values were log-transformed for repeated measures analysis (except for fetal heart rate). If there were significant interactions between the group and time of study period, the Student's t test was used for further analysis. The association between fetal heart rate or fetal heart rate variability (dependent variables) and gestational age, birthweight and cord arterial pH value (continuous independent variables) were analysed with the linear model for repeated measures. Time of study period was used as repeated factor in linear models. The clinical data were analysed with the Student's t test, Wilcoxon two-sample test or Fisher's exact test, as appropriate. The results are expressed as mean (range) or median [range], as appropriate. $P < 0.05$ was considered significant. Statistical analysis was performed with SAS System for Windows, release 8.01 (SAS Institute, Cary, North Carolina, USA).

RESULTS

We found that during the last hour of monitoring, baseline fetal heart rate gradually decreased, whereas spectral band densities assessing total fetal heart rate variability, low-frequency and high-frequency fetal heart rate variability first gradually increased but then dropped near the delivery in the acidotic fetuses when compared with the controls (Figs 1 and 2). Low-to-high frequency ratio was greater in the acidotic group during the whole study period ($P = 0.002$, Fig. 2) due to a predominant rise in low-frequency fetal heart rate variability.

The cord arterial pH from all fetuses was inversely associated with total fetal heart rate variability ($P < 0.001$), low-frequency fetal heart rate variability ($P < 0.001$) and low-to-high frequency ratio ($P = 0.004$). There was a significant interaction between time of the study period and cord arterial pH in high-frequency fetal heart rate variability ($P = 0.007$), suggesting that the association between high-frequency fetal heart rate variability and cord arterial pH was not the same over the last hour of the

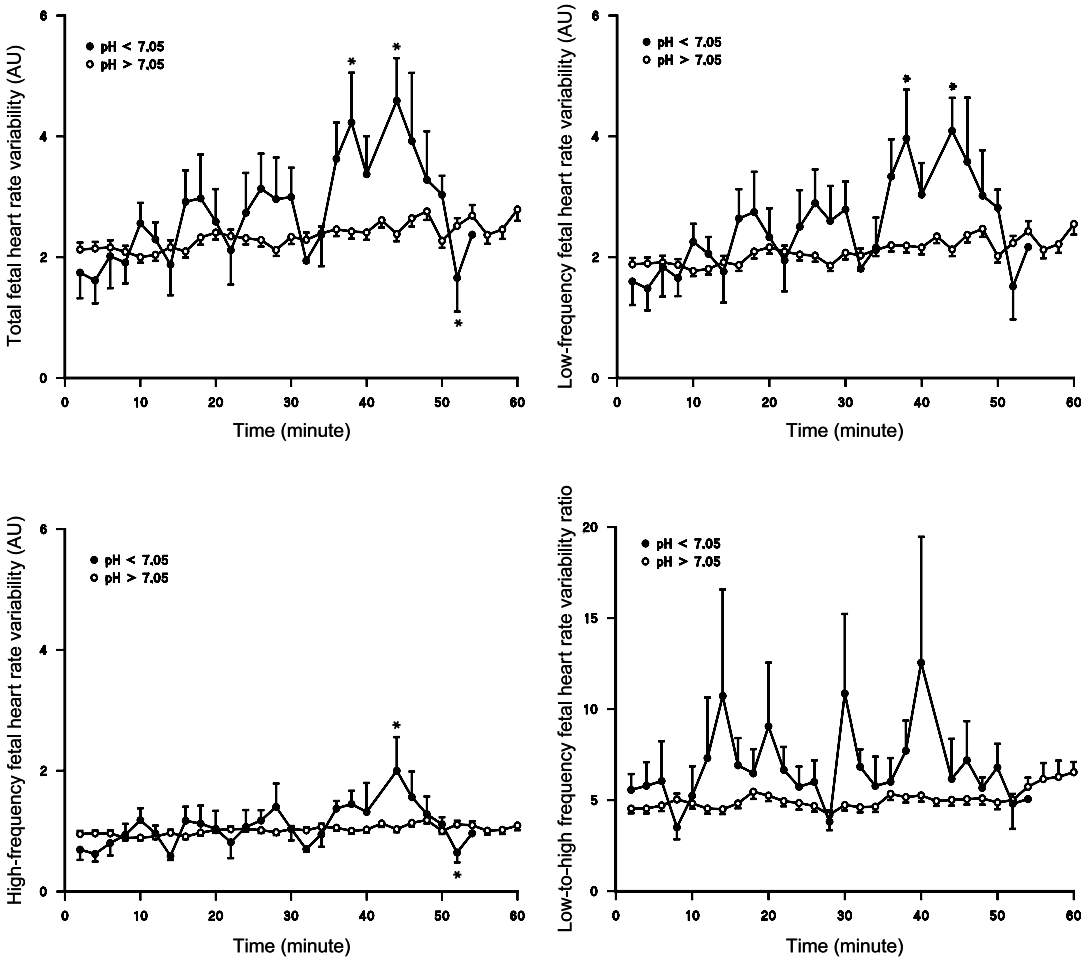

Fig. 2. Fetal heart rate variability in different spectral frequency bands during the last hour of labour in the acidotic fetuses (pH < 7.05) and the control fetuses (pH ≥ 7.05). There was a significant interaction between the study groups and time of the study period in total fetal heart rate variability ($P = 0.018$), low-frequency fetal heart rate variability ($P = 0.03$) and high-frequency fetal heart rate variability ($P = 0.009$; ANOVA for repeated measures). The low-to-high frequency ratio was greater in the acidotic group than in the control group ($P = 0.002$) and no significant interaction was observed. The spectral components of fetal heart rate variability are presented in arbitrary units (AU). * = significant difference between groups ($P < 0.05$; two-sample t test).

recording. High-frequency fetal heart rate variability was positively associated with gestational age ($P = 0.044$) and negatively associated with birthweight ($P = 0.043$) in contrast to the other parameters studied showing no associations with gestational age or birthweight.

CONCLUSIONS

We found that during the last hour of delivery, fetal heart rate gradually decreased, whereas fetal heart rate variability initially increased but then gradually dropped as labour progressed in acidotic fetuses. To test how marked acidosis would influence fetal heart rate variability, a cutoff point of cord artery pH of 7.05 was chosen. This is a level of acidosis known to expose the fetus to a risk of neonatal symptoms. Also, it has been applied as a marker of significant acidosis in previous studies on intrapartum asphyxia.[9,13,14]

In the human fetus, acute hypoxia causes a small increase in fetal heart rate, but in severe acidosis fetal heart rate gradually declines, resulting in bradycardia.[15,16] The reduction in fetal heart rate variability in the presence of bradycardia appears to be a rather late sign of severe acidosis,[5,17] and is associated with reduced cerebral oxygen consumption and poor fetal outcome.[16,18] Although there are significant

non-neural influences, it appears that a large proportion of fetal heart rate variability may be explained by centrally mediated fluctuations in the autonomic nervous system.[19] However, specific fetal heart rate patterns associated with developing hypoxia in labour remain largely unknown.

Recently, data in a large randomised controlled trial have shown the ability of automatic ST waveform analysis to provide a warning in situations of developing hypoxia and acidosis, thus substantially reducing the risk of term neonates being affected by adverse events in labour.[14] The current database have been analysed in another study regarding ST waveform changes in fetal ECG.[9] All the acidotic fetuses displayed an increase in T/QRS ratio coinciding in time with the increase in low-frequency fetal heart rate variability. Such an ST pattern is associated with enhanced β-adrenoceptor activity and an adrenaline surge.[20,21]

Spectral analysis provides a tool for quantifying rather small changes in fetal heart rate variability that may remain undetected if only visual interpretation of fetal heart rate tracings is used. In the spectrum, we can examine the simultaneously occurring slow and fast fetal heart rate oscillations and estimate changes in both sympathetic and parasympathetic control of the autonomic nervous system. In our study, the initial increase observed in total fetal heart rate variability was composed mainly of an increase in low-frequency fetal heart rate variability. This is mainly due to sympathetic activation,[5] but parasympathetic activity also contributes to increased low-frequency variation as shown in adults.[11] In fetuses, however, the sympathetic system predominates and it is active earlier in fetal life than the parasympathetic system becoming more prominent with advancing maturity.[22] This was further corroborated in this study showing a positive association between high-frequency fetal heart rate variability and the gestational age of the fetuses studied. Finally, in the acidotic fetuses, sympathetic predominance was also reflected in the increased low-to-high frequency ratio, which is a sign of increased sympathetic activation according to experimental studies.[23] On the other hand, the decrease in fetal heart rate variability, following an initial increase, observed in the acidotic group, may represent an initial sign of decompensation of the circulatory system during marked acidosis. Probably largely depending on the diminishing number of signal segment samples toward the end of the delivery, the decrease in fetal heart rate variability was significant only in total fetal heart rate variability. The tendency was, however, seen also in low-frequency and high-frequency fetal heart rate variability, as well as in low-to-high frequency ratio.

Because the fetal heart rate and fetal heart rate variability are also dependent on each other, in our study all the fetal heart rate variability data were corrected for baseline heart rate.[12] Several additional factors such as gestational age, fetal activity, uterine contractions and medication also modify fetal heart rate variability. In our study, gestational age showed no association with low-frequency or total fetal heart rate variability probably because only pregnancies over 35 weeks were included. Fetal movements may increase low-frequency fetal heart rate variability, but there have also been contradictory results.[24,25] During delivery, fetal movements decrease and, when they do occur, they are mostly associated with uterine contractions.[26,27] During acidosis, the number of fetal movements further decreases.[26] Therefore, the observed increase in low-frequency fetal heart rate is unlikely to be caused by fetal movements. To what extent contractions *per se* may cause enhanced fetal sympathetic activity is unclear.[19] However, they are unlikely to influence our results, because we studied fetal heart rate variability in 2-minute signal segments. A contraction should take place at least three times within a 2-minute signal segment in order to be detected by spectral analysis. Finally, epidural or spinal analgesia may cause minimal changes in fetal heart rate.[28] These changes are, however, transient and resolve within 30 minutes,[29] and only tracings from the last hour of delivery were included in this study.

In conclusion, our results suggest that changes in fetal heart rate variability as measured by spectral band densities, together with decreased fetal heart rate during the last hour of delivery, reflect problems of autonomic cardiac control in mature fetuses responding to the stress of labour. The current data show feasibility of quantifying fetal heart rate variability to assist in the interpretation of complex fetal heart rate patterns. However, the number of acidotic fetuses was rather small for far-reaching conclusions on clinical applicability. Our results give an indication that spectral analysis of fetal heart rate variability gives additional information for identification of acidotic fetuses along with standard cardiotocography and fetal ECG.

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References

1. Spencer JA. Clinical overview of cardiotocography. *Br J Obstet Gynaecol* 1993;**100**(Suppl 9):4–7.
2. Blix E, Sviggum O, Koss KS, Øian P. Inter-observer variation in assessment of 845 labour admission tests: comparison between midwives and obstetricians in the clinical setting and two experts. *Br J Obstet Gynaecol* 2003;**110**(1):1–5.
3. Dawes GS, Lobb M, Moulden M, Redman CW, Wheeler T. Antenatal cardiotocogram quality and interpretation using computers. *Br J Obstet Gynaecol* 1992;**99**(10):791–797.

4. Dawes G, Meir YJ, Mandruzzato GP. Computerized evaluation of fetal heart-rate patterns. *J Perinat Med* 1994;**22**(6):491–499.
5. van Ravenswaaij-Arts CM, Kollée LA, Hopman JC, Stoelinga GB, van Geijn HP. Heart rate variability. *Ann Intern Med* 1993;**118**(6): 436–447.
6. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981;**213**(4504): 220–222.
7. Sibony O, Fouillot JP, Benaoudia M, et al. Quantification of the fetal heart rate variability by spectral analysis of fetal well-being and fetal distress. *Eur J Obstet Gynecol Reprod Biol* 1994;**54**(2):103–108.
8. Siimes AS, Välimäki IA, Antila KJ, et al. Regulation of heart rate variation by the autonomic nervous system in neonatal lambs. *Pediatr Res* 1990;**27**(4 Pt 1):383–391.
9. Amer-Wåhlin I, Bördahl P, Eikeland T, et al. ST analysis of the fetal electrocardiogram during labor: Nordic observational multicenter study. *J Matern Fetal Neonatal Med* 2002;**12**(4):260–266.
10. Välimäki I, Rantonen T. Spectral analysis of heart rate and blood pressure variability. *Clin Perinatol* 1999;**26**(4):967–980.
11. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;**93**(5):1043–1065.
12. Hayano J, Sakakibara Y, Yamada M, et al. Diurnal variations in vagal and sympathetic cardiac control. *Am J Physiol* 1990;**258**(3 Pt 2): H642–H646.
13. Goldaber KG, Gilstrap III LC, Leveno KJ, Dax JS. Pathologic fetal acidemia. *Obstet Gynecol* 1991;**78**(6):1103–1107.
14. Norén H, Amer-Wåhlin I, Hagberg H, et al. Fetal electrocardiography in labor and neonatal outcome: data from the Swedish randomized controlled trial on intrapartum fetal monitoring. *Am J Obstet Gynecol* 2003;**188**(1):183–192.
15. Thaler I, Timor-Tritsch IE, Blumenfeld Z. Effect of acute hypoxia on human fetal heart rate. The significance of increased heart rate variability. *Acta Obstet Gynecol Scand* 1985;**64**(1):47–50.
16. Williams KP, Galerneau F. Fetal heart rate parameters predictive of neonatal outcome in the presence of a prolonged deceleration. *Obstet Gynecol* 2002;**100**(5 Pt 1):951–954.
17. Ribbert LS, Snijders RJ, Nicolaides KH, Visser GH. Relation of fetal blood gases and data from computer-assisted analysis of fetal heart rate patterns in small for gestation fetuses. *Br J Obstet Gynaecol* 1991;**98**(8):820–823.
18. Field DR, Parer JT, Auslender R, Baker BW, Ross BK, Leicht CH. Fetal heart rate variability and cerebral oxygen consumption in fetal sheep during asphyxia. *Eur J Obstet Gynecol Reprod Biol* 1991; **42**(2):145–153.
19. Oppenheimer LW, Lewinsky RM. Power spectral analysis of fetal heart rate. *Bailliere's Clin Obstet Gynaecol* 1994;**8**(3):643–661.
20. Rosén KG, Dagbjartsson A, Henriksson BÅ, Lagercrantz H, Kjellmer I. The relationship between circulating catecholamines and ST waveform in the fetal lamb electrocardiogram during hypoxia. *Am J Obstet Gynecol* 1984;**149**(2):190–195.
21. Dagbjartsson A, Herbertsson G, Stefansson TS, Kjeld M, Lagercrantz H, Rosén KG. Beta-adrenoceptor agonists and hypoxia in sheep fetuses. *Acta Physiol Scand* 1989;**137**(2):291–299.
22. Assali NS, Brinkman III CR, Woods Jr JR, Dandavino A, Nuwayhid B. Development of neurohumoral control of fetal, neonatal, and adult cardiovascular functions. *Am J Obstet Gynecol* 1977;**129**(7): 748–759.
23. Metsälä T, Siimes A, Välimäki I. The effect of change in sympatho-vagal balance on heart rate and blood pressure variability in the foetal lamb. *Acta Physiol Scand* 1995;**154**(2):85–92.
24. Breborowicz G, Moczko J, Gadzinowski J. Quantification of the fetal heart rate variability by spectral analysis in growth-retarded fetuses. *Gynecol Obstet Investig* 1988;**25**(3):186–191.
25. Zimmer EZ, Divon MY, Vadasz A. Fetal heart rate beat-to-beat variability in uncomplicated labor. *Gynecol Obstet Investig* 1988; **25**(2):80–82.
26. Natale R, Clewlow F, Dawes GS. Measurement of fetal forelimb movements in the lamb in utero. *Am J Obstet Gynecol* 1981;**140**(5): 545–551.
27. Wittmann BK, Davison BM, Lyons E, Frohlich J, Towell ME. Real-time ultrasound observation of fetal activity in labour. *Br J Obstet Gynaecol* 1979;**86**(4):278–281.
28. Capogna G. Effect of epidural analgesia on the fetal heart rate. *Eur J Obstet Gynecol Reprod Biol* 2001;**98**(2):160–164.
29. Palmer CM, Maciulla JE, Cork RC, Nogami WM, Gossler K, Alves D. The incidence of fetal heart rate changes after intrathecal fentanyl labor analgesia. *Anesth Analg* 1999;**88**(3):577–581.

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Change in heart rate variability in relation to a significant ST-event associates with newborn metabolic acidosis

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Objective To find whether low-to-high frequency (LF/HF) ratio of fetal heart rate (FHR) variability changes in relation to a significant ST-event during delivery, and if the change is predictive of metabolic acidosis of the newborn.

Design A case–control study.

Setting Data from a multicentre project.

Subjects Acidotic and control fetuses with abnormal cardiotocography together with a ST-event in fetal electrocardiogram (ECG).

Methods We studied intrapartum FHR variability with spectral analysis from 34 fetuses with a significant ST-event in the fetal ECG. LF/HF ratio of FHR variability was measured within a period of 1 hour before and 1 hour after a significant ST-event. Sensitivity and specificity of the change in LF/HF ratio of FHR variability in prediction of metabolic acidosis ($pH \leq 7.05$ and base deficit value > 12.0 mmol/l) of the newborn were described by means of the receiver operating characteristic curve.

Main outcome measures Change in LF/HF ratio of FHR in relation to a significant ST-event.

Results We found that a relative change in LF/HF ratio greater than 30% in relation to a significant ST-event predicted cord arterial metabolic acidosis with a sensitivity of 89% (95% CI 68–100%) and specificity of 80% (95% CI 64–96%).

Conclusions Relative changes in LF/HF ratio of FHR variability in relation to a significant ST-event are more pronounced in fetuses born with metabolic acidosis.

Keywords Fetal electrocardiography, fetal heart rate variability, labour, metabolic acidosis, power spectra, ST-event.

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Introduction

Assessment of fetal wellbeing during delivery is complex. The specificity of abnormal cardiotocography (CTG) is low in revealing hypoxia. Thus, additional information is needed. Oxygen deficiency may cause a rise in the ST waveform of the fetal electrocardiogram (ECG). This rise has been shown to be associated with anaerobic myocardial metabolism and related to a surge in adrenaline as part of fetal response to hypoxia.[1,2] Currently, conventional fetal heart rate (FHR) features in conjunction with automatic ST analysis of the fetal ECG are used to indicate abnormality. This has been shown to reduce both the rates of operative deliveries for fetal distress and metabolic acidosis during birth.[3,4] The cardiovascular response to hypoxia in the fetus depends on fetal reserves and the severity of hypoxia.[5] Besides hypoxia, there are physiological reasons behind an ST rise. Arousal reactions may increase myocardial workload and cause a rise in ST segment of fetal ECG.[6] Therefore, more detailed information on the origin of fetal reactions may be useful.

Oxygen deficiency activates autonomic nervous system and causes changes in FHR and FHR variability.[7] Power spectral analysis can be used to detect and quantify these changes. Low-to-high frequency (LF/HF) ratio may serve as a FHR variability marker to assess fetal metabolic acidosis during delivery.[8] The aim of this study was to find if fetuses with metabolic acidosis could be identified by measuring a change in LF/HF ratio of FHR variability at the time of a significant ST-event in fetal ECG.

Materials and methods

ECG recordings of 911 fetuses with cord artery acid–base status measured after birth were collected as a part of a multicentre project on intrapartum fetal monitoring between October 2000 and June 2002.[9] Fetal ECG was recorded and analysed with STAN software (STAN®, Neoventa Medical, Moelndal, Sweden), which provides automatic analysis of the ST interval of fetal ECG.[3,10] Based on the STAN clinical guidelines,[9] an intermediary or abnormal CTG together with a ST change is considered as a significant ST-event. Of all acidotic fetuses (pH ≤ 7.05; n = 52) of the original data, we selected those acidotic fetuses having a significant ST-event in fetal ECG and more than 10 minutes good quality ECG recording both before and after the first significant ST-event (n = 22). Metabolic acidosis was defined as both a cord artery pH ≤ 7.05 and a base deficit value (BDecf) > 12.0 mmol/l. A control fetus for every acidotic fetus in the original data was chosen as the next fetus delivered within the same labour ward with a cord arterial pH ≥ 7.20 and BDecf < 8 mmol/l (n = 51). Of these fetuses, we selected those control fetuses that had a significant ST-event in fetal ECG and more than 10 minutes good quality ECG recording both before and after the first significant ST-event (n = 12). The median time lag between the first significant ST-event and delivery was 48 minutes (range 11–536 minutes, no difference between the study groups, P = 0.69). An ST-event was due to an increase in T-wave amplitude (ST rise) in 31 fetuses and due to biphasic ST segments in 3 of the 34 studied fetuses. Selection of the studied fetuses is shown in Figure 1. None of the fetuses had major cardiac anomalies. Clinical data of the studied fetuses are shown in Table 1. Ethical approval and informed consent was obtained in those centres where STAN was not being used as part of standard care.

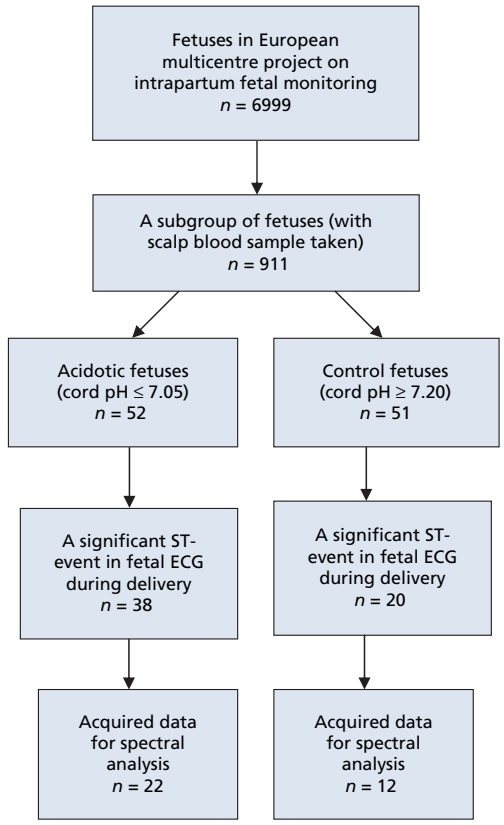

Figure 1. Selection of the studied fetuses.

Data acquisition and signal processing

Fetal ECG was recorded with an intrauterine scalp electrode using a STAN®S 21 monitor. Fetal unipolar ECG lead configuration consisted of a single helix scalp electrode and a maternal skin electrode. R-peaks were detected, and R-R intervals were measured and digitised at a sampling rate of 500 Hz. The R-R interval data sets were stored digitally as part of STAN data archiving, and the intervals from the study period were analysed off-line.

LF/HF ratio

The LF/HF ratio of FHR variability[11] was measured with spectral analysis in 2-minute segments from a period of 1 hour before and 1 hour after a significant ST-event or until delivery. On average, 22 continuous 2-minute segments were obtained from each fetus. The quality of these segments was checked by a signal analyst, and data analysis was performed with no knowledge on the clinical details of the fetuses. In the case of large signal breaks in 2-minute R-R data segment, a new segment was started immediately after a break. The R-R interval data sets were transformed to a continuous digital signal by linear interpolation, and the reciprocal of each R-R interval was computed to obtain the respective instantaneous heart rate reading. Fast-Fourier-Transformed power spectra was computed for the FHR signal segments (MATLAB®-oriented tailor-made signal analysis program, MARAPS, Tampere, Finland).[12]

For calculation of LF/HF ratio of FHR variability, power spectrum was integrated over the low-frequency band from 0.04 to 0.15 Hz (from 2.4 to 7.8 cycles/minutes) and over the high-frequency band from 0.15 to 1.0 Hz (from 7.8 to 60 cycles/minutes). To minimise the effect of FHR to FHR variability, we calculated the coefficient of component variance (square root of power spectra/mean R-R interval).[13]

Statistical methods

For each fetus, a relative change in LF/HF ratio was calculated ([median LF/HF_{after}–median LF/HF_{before}]/median LF/HF_{before}) in association to a significant ST-event. The best cutoff value to find those fetuses showing metabolic acidosis

Table 1. Clinical data of the studied fetuses. Values are expressed as mean (range) or median [range] unless stated otherwise. *P* = statistical significance for intergroup difference

	Acidotic fetuses (*n* = 22)	Control fetuses (*n* = 12)	*P*-value
Gestational age, weeks	40.5 [37–43]	40 [38–42]	0.91*
Birthweight, g	3576 (2545–4600)	3409 (2505–4250)	0.37**
Number of operational deliveries	14	7	1.00***
5-minute Apgar score	8 [4–10]	10 [9–10]	0.003*
Cord arterial pH	6.99 (6.89–7.04)	7.24 (7.21–7.29)	<0.0001**
Cord arterial BDecf, mmol/l	11.7 (4.6–20.0)	4.5 (0.3–7.8)	<0.0001**

*Wilcoxon two-sample test.
**Two-sample *t* test.
***Fisher's exact test.

during birth was determined by a receiver operating characteristic (ROC) curve. The 95% CIs for sensitivity and specificity were calculated based on the binomial proportion. Logistic regression analysis was performed to test whether the same cutoff value can be used for both an increase and a decrease in LF/HF ratio. The background characteristics of the fetuses were tested with Fisher's exact test, Student's *t* test or Wilcoxon two-sample test, as appropriate. The results are expressed as mean (range) or median [range]. *P*-value < 0.05 was considered significant. Statistical analysis was performed with SAS System for Windows, release 8.01 (SAS Institute, Cary, NC, USA).

Results

Greater than 30% change in relative LF/HF ratio of FHR variability in relation to a significant ST-event was associated with cord arterial metabolic acidosis. The sensitivity of this change in prediction of metabolic acidosis was 89% (95% CI 68–100%) and specificity 80% (95% CI 64–96%) (Figure 2). Only one of nine newborns with metabolic acidosis was not identified with this cutoff value, whereas two control cases with pH ≥ 7.20 revealed marked LF/HF change. Three fetuses with greater than 30% increase in relative LH/HF ratio that did not have metabolic acidosis showed a low pH < 7.05 and BDecf 8.5, 10.6 and 10.9 mmol/l during birth. The relative changes in LF/HF ratio associated to cord arterial BDecfs are shown in Figure 3. Clinical characteristics of the fetuses are shown in Table 2.

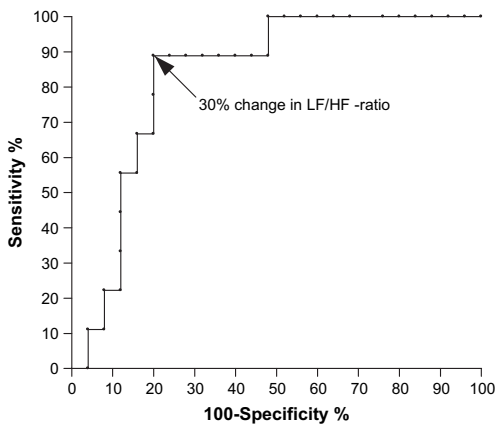

Figure 2. ROC curve of the relative change in LF/HF ratio of FHR variability in relation to a significant ST-event in prediction of cord arterial metabolic acidosis.

Discussion

We found that a relative change in LF/HF ratio of FHR variability greater than 30% in relation to a significant ST-event is associated with cord artery metabolic acidosis.

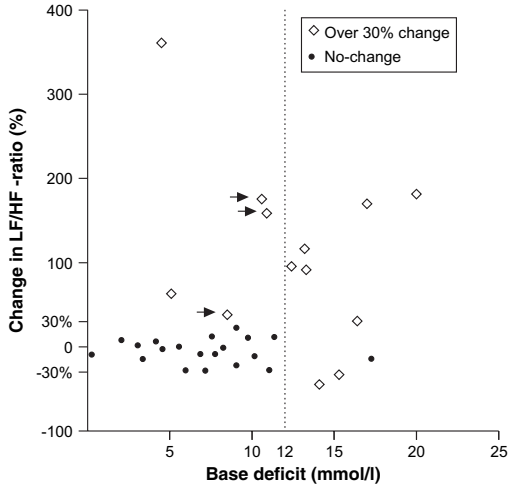

Figure 3. The relative change in spectral powers of LF/HF ratio of FHR variability associated with a significant ST-event correlated with cord arterial BDecfs in the studied fetuses (*n* = 34). Cases marked with an arrow represent a fetus with pH ≤ 7.05 but BDecf < 12 mmol/l during birth.

Table 2. Comparison of the fetuses with significant change (greater than 30%) or nonsignificant change (less than 30%) in LF/HF ratio of FHR variability. Values are expressed as mean (range) or median [range] unless stated otherwise. *P* = statistical significance for intergroup difference by analysis of variance

	LF/HF change groups		
	Greater than 30% change (*n* = 13)	**No change (*n* = 21)**	***P*-value**
Gestational age, weeks	40 [38–42]	40 [37–43]	0.50*
Birthweight, g	3468 (2545–4250)	3547 (2505–4600)	0.66**
Cord arterial pH	6.97 [6.92–7.23]	7.04 [6.89–7.29]	0.004*
Cord arterial BDecf, mmol/l	12.41 (4.50–20.0)	7.26 (0.30–17.30)	0.001**
5-minute Apgar score	8 [4–10]	9 [4–10]	0.09*
Number of operational deliveries	10	11	0.28***
Neonatal surveillance (%)	7 (54)	6 (29)	0.17***

*Wilcoxon two-sample test.
**Two-sample *t* test.
***Fisher's exact test.

During delivery, making a decision to intervene is subjective and affected by several factors. The inter-observer agreement has been found to be higher when CTG is interpreted together with ST waveform analysis than alone, and interventions have been shown to be more appropriate.[14,15] However, the CTG interpretation is still subjective with the risk of patterns being misinterpreted.

To assess the impact of hypoxia on FHR variability and ECG is complicated, not only from a clinical perspective but also considering the variety in physiological responses. Based on our current understanding, there are two key features to be addressed: first, alterations in autonomic nervous tone as reflected by beat-to-beat variations; and second, ability of the fetal myocardium to respond to an increase in myocardial workload and hypoxia.

Experimental studies have shown that progressive metabolic acidosis due to repeated umbilical cord occlusions leads to either an increase or a decrease in FHR variability.[16] It has been previously suggested that power spectral analysis of FHR variability could be a more sensitive indicator of fetal wellbeing than other methods based on FHR.[17] Further, it has been found that acute hypoxaemia due to umbilical artery embolism has been associated with increased relative power (percent of total power) in low-frequency FHR variability and decreased relative power in high-frequency range in fetal sheep,[18] thus leading to an increased LF/HF ratio. We have previously shown that in human fetuses the LF/HF ratio of FHR variability is superior to other spectral measures in detection of fetal metabolic acidosis during the last hour of labour.[8]

Metabolic changes in the heart muscle are reflected as ST changes in fetal ECG.[1,19] As observed in this study, ST changes may also be seen in nonhypoxic fetuses as a consequence of arousal reactions.[4,14] According to the study protocol, all the fetuses had a significant ST-event during delivery, but only 9 of 34 (26%) had metabolic acidosis during birth. In case there was a significant change in the LF/HF ratio of FHR variability together with a significant ST-event, 62% of the fetuses had metabolic acidosis (pH ≤ 7.05 and BDecf > 12.0 mmol/l) and 85% had cord arterial pH ≤ 7.05 during birth. Therefore, spectral analysis of FHR variability may provide clinically relevant information of fetal wellbeing and may help differentiate between physiologic ST changes from hypoxic ST changes. In clinical situations, the sensitivity of this method needs to be tested.

From the methodological point of view, spectral analysis of FHR variability during labour requires a stationary signal, and for calculation of low-frequency variability, a continuous signal segment of at least 75 seconds is needed. This is a shortcoming also in this data, because during delivery, the FHR is often nonstationary with large fluctuations due to uterine and fetal activity. An advantage is that R-R interval data are freely available for spectral calculations whenever fetal ECG is recorded.

In conclusion, this study suggests that a relative change in LF/HF ratio greater than 30% in association with a significant ST-event in fetal ECG predicts cord arterial metabolic acidosis and assists in separating hypoxic ST events from physiological arousal reactions. This additional information on fetal wellbeing may help prevent unnecessary operational deliveries. Further studies on this method in a larger material would be of interest.

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References

1 Greene KR, Dawes GS, Lilja H, Rosén KG. Changes in the ST waveform of the fetal lamb electrocardiogram with hypoxemia. *Am J Obstet Gynecol* 1982;144:950–8.

2 Rosén KG, Dagbjartsson A, Henriksson BA, Lagercrantz H, Kjellmer I. The relationship between circulating catecholamines and ST waveform in the fetal lamb electrocardiogram during hypoxia. *Am J Obstet Gynecol* 1984;149:190–5.

3 Amer-Wåhlin I, Hellsten C, Norén H, Hagberg H, Herbst A, Kjellmer I, *et al*. Cardiotocography only versus cardiotocography plus ST analysis of fetal electrocardiogram for intrapartum fetal monitoring: a Swedish randomised controlled trial. *Lancet* 2001;358:534–8.

4 Westgate J, Harris M, Curnow JS, Greene KR. Plymouth randomized trial of cardiotocogram only versus ST waveform plus cardiotocogram for intrapartum monitoring in 2400 cases. *Am J Obstet Gynecol* 1993;169:1151–60.

5 Richardson BS, Bocking AD. Metabolic and circulatory adaptations to chronic hypoxia in the fetus. *Comp Biochem Physiol A Mol Integr Physiol* 1998;119:717–23.

6 Dagbjartsson A, Herbertsson G, Stefansson TS, Kjeld M, Lagercrantz H, Rosén KG. Beta-adrenoceptor agonists and hypoxia in sheep fetuses. *Acta Physiol Scand* 1989;137:291–9.

7 van Ravenswaaij-Arts CM, Kollée LA, Hopman JC, Stoelinga GB, van Geijn HP. Heart rate variability. *Ann Intern Med* 1993;118:436–47.

8 Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Välimäki IA, Rosén KG, *et al*. Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. *BJOG* 2005;112:418–23.

9 Luttkus AK, Norén H, Stupin JH, Blad S, Arulkumaran S, Erkkola R, *et al*. Fetal scalp pH and ST analysis of the fetal ECG as an adjunct to CTG. A multi-center, observational study. *J Perinat Med* 2004;32:486–94.

10 Amer-Wåhlin I, Bördahl P, Eikeland T, Hellsten C, Norén H, Sörnes T, *et al*. ST analysis of the fetal electrocardiogram during labor: Nordic observational multicenter study. *J Matern Fetal Neonatal Med* 2002; 12:260–6.

11 Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996;93:1043–65.

12 Välimäki I, Rantonen T. Spectral analysis of heart rate and blood pressure variability. *Clin Perinatol* 1999;26:967–80.

13 Hayano J, Sakakibara Y, Yamada M, Kamiya T, Fujinami T, Yokoyama K, *et al*. Diurnal variations in vagal and sympathetic cardiac control. *Am J Physiol* 1990;258:H642–6.

14 Amer-Wåhlin I, Ingemarsson I, Marsal K, Herbst A. Fetal heart rate patterns and ECG ST segment changes preceding metabolic acidaemia at birth. *BJOG* 2005;112:160–5.

15 Olofsson P. Current status of intrapartum fetal monitoring: cardiotocography versus cardiotocography + ST analysis of the fetal ECG. *Eur J Obstet Gynecol Reprod Biol* 2003;110(Suppl 1):S113–18.

16 Westgate JA, Bennet L, Gunn AJ. Fetal heart rate variability changes during brief repeated umbilical cord occlusion in near term fetal sheep. *Br J Obstet Gynaecol* 1999;106:664–71.

17 Oppenheimer LW, Lewinsky RM. Power spectral analysis of fetal heart rate. *Baillieres Clin Obstet Gynaecol* 1994;8:643–61.

18 Li X, Tang D, Zhou S, Zhou G, Wang C, Zhuang Y, *et al*. Redistribution of power spectrum of heart rate variability during acute umbilical artery embolism and hypoxemia in late-gestation fetal sheep. *Eur J Obstet Gynecol Reprod Biol* 2004;114:137–43.

19 Rosén KG, Hökegård KH, Kjellmer I. A study of the relationship between the electrocardiogram and hemodynamics in the fetal lamb during asphyxia. *Acta Physiol Scand* 1976;98:275–84.

Do spectral bands of fetal heart rate variability associate with concomitant fetal scalp pH?

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Abstract

Objective: To establish the association between fetal scalp blood sample (FBS) pH-value and spectral powers of intrapartum fetal heart rate (FHR) variability.

Design: Retrospective observational clinical study

Setting: Data from an EU multicenter project

Population: 462 fetuses who had a normal pH-value (pH >7.20; controls) in scalp blood sample and 81 fetuses who had a low scalp pH-value (≤ 7.20; low-FBSpH -fetuses). The low-FBSpH-fetuses were further divided into two subgroups according to the degree of acidemia: fetuses with FBS pH 7.11–7.20 (n = 58) and fetuses with FBS pH ≤ 7.10 (n = 23)

Methods: FHR variability was measured with power spectral analysis from a period of 14 minutes preceding last FBS. In addition two groups with two measure points were chosen: in the first group (108 fetuses), both the first and the last FBS pH were normal, and in the second group (40 fetuses) the initial FBS pH was or the 30 min CTG segment at the beginning of the recording was normal but the last FBS pH-value was low (pH ≤ 7.20).

Main outcome measures: Changes in spectral powers in the course of labor. FHR variability in relation to concomitant FBS pH-value.

Results: In the course of labor, spectral powers of FHR variability increased in all fetuses, but fetuses with FBS pH ≤ 7.20 had more increased spectral powers of FHR variability compared with controls (2.49 AU vs. 2.23 AU; p = 0.038). Further, the overall FHR variability was higher in low-FBSpH -fetuses when compared with control fetuses. Interestingly, the fetuses with the lowest FBS pH (≤ 7.10) had significantly lower spectral powers when compared to fetuses with FBS in the pH-range 7.11-7.20 (1.42 AU vs. 1.59 AU; p = 0.047). There was no clinically relevant correlation between spectral powers of FHR variability and FBS pH-values.

Conclusions: This study shows that intrapartum spectral powers of FHR variability are altered during delivery, and especially with developing fetal acidosis. Further, decreasing spectral powers of FHR variability may be due to an attenuation of the cardiovascular defense of the fetus.

Introduction

Detection of fetal asphyxia during labor and delivery is challenging. A normal and reactive cardiotocograph (CTG) is reassuring, indicating no obvious danger of asphyxia. Unfortunately, CTG is unspecific, with a great number of false positive findings leading to increased numbers of unnecessary operational deliveries (1).

Fetal scalp pH aids in the identification of intrapartum fetal hypoxia. CTG can be used for screening tool; FBS is taken under certain conditions when the CTG is non-reassuring (2). FBS gives only momentary information of fetal wellbeing (concerning oxygenation), and needs often to be taken repeatedly. FBS is time-consuming and inconvenient to the parturient and may lead to complications. The incidence of complications ranges from 0.4 to 6 %. Most complications due to FBS are insignificant, although exceptional cases of neonatal death due to bleeding from the incision wound have been reported (3,4) ST analysis of the fetal electrocardiogram (ECG) is used in combination with CTG to assess fetal well-being during delivery. Compared to FBS, ST-analysis (STAN®) yields continuous information and is more convenient for the parturient. However, the STAN® methodology is dependent on interpretation of the CTG, which has high inter- and intraobserver variability, especially on nonreassuring FHR tracings (5). Thus, more objective information on specific FHR parameters would be advantageous, and would facilitate the interpretation of fetal responses to hypoxia.

In late pregnancy, the fetal autonomic nervous system responds to acute hypoxia by modulating beat-to-beat FHR changes. Visual FHR variability pattern recognition and clinical interpretation are mostly subjective. Heart rate fluctuations (5-25 bpm) around baseline FHR, known as FHR variability, indicate normal fetal reactivity (6). Short-term, beat-to-beat FHR variations remain undetected. Power spectral analysis of FHR variability is an objective method to quantify small, visually undetectable changes in FHR variability that are under autonomic cardiac control (7,8). Previous studies have shown that low-frequency (LF) spectral power corresponding to parasympathetic and sympathetic activity, and high-frequency (HF) spectral power corresponding to parasympathetic activity, change markedly in fetuses with birth acidemia (9,10). Further, a change in the low-to-high frequency ratio (LF/HF) of FHR variability in relation to a STAN® alarm predicts fetal metabolic acidemia at birth (11).

Previous studies on intrapartum FHR variability measured with power spectral analysis have mainly assessed changes of FHR variability in relation to cord acid base values measured after birth. The aim of the present study was to investigate the effect of intrapartum hypoxia and acidemia on FHR variability. The correlation between spectral powers and the concomitant FBS pH-value was calculated to examine how FHR variability associates with fetal intrapartum pH-values. Further, the change in spectral powers of FHR variability during labor was assessed in fetuses with repeatedly normal FBS pH-values, and in fetuses with a low last FBS pH-value.

Materials and methods

The original data consisted of 812 fetuses with intrapartum ECG (R-R interval data) recorded as a part of an EU multicenter project on intrapartum fetal monitoring with STAN® method (12). From these data, those fetuses (n=543) having good quality (e.g. no large breaks) ECG recorded 15

minutes prior to last FBS with no cardiac or major extra-cardiac malformation were included. Duration of pregnancies exceeded 36 weeks. Ethical approval and informed consent were obtained in those centers where STAN® was not being used as part of standard care.

FHR variability data was divided according to the scalp blood pH-value: FBS pH ≤ 7.20 is regarded as a sign of increased risk of fetal acidosis (13), and was thereby selected as a cut-off value. Study data was comprised of 462 fetuses with scalp pH >7.20 (controls) and 81 fetuses with scalp pH ≤ 7.20 (low-FBSpH -fetuses). The low-FBSpH -fetuses were further divided into two subgroups based on how low the FBS pH was: fetuses with FBS pH 7.11-7.20 (n= 58) and fetuses with FBS pH ≤ 7.10 (n=23). A flow chart on the process of selection of cases is presented in Fig.1.

We also studied how FHR variability changes during labor and delivery in two additional groups with two measure points during delivery: in the first group (108 fetuses), both the first and the last FBS pH were normal, and in the second group (40 fetuses) the initial FBS pH was or the 30 min CTG segment at the beginning of the recording was normal but the last-FBS pH-value was low (pH ≤ 7.20).(the interval between the end of normal CTG segment and last FBS was over 75 minutes).

Data acquisition and signal processing. Fetal ECG was recorded during delivery with an intrauterine scalp electrode using a STAN®S 21 monitor (Neoventa Medical, Moelndal, Sweden). Fetal unipolar ECG lead configuration consisted of a single-helix scalp electrode and a maternal skin electrode. R-peaks were detected, and R-R intervals were measured and digitized at a sampling rate of 500 Hz. The R-R interval data sets were stored digitally as part of STAN data archiving, and the intervals from the study period were analyzed off-line.

Spectral analysis. FHR variability was quantified with spectral analysis as previously described (9,11,14). Power spectral analysis was performed in 2-minute signal segments from a period of 14 minutes (7x2min) preceding the FBS. On average, four continuous 2-minute signal segments were obtained, and mean spectral power of these segments was calculated. The quality of these signal segments was checked by a signal analyst, and data analysis was performed with no knowledge on the clinical data. In the case of large signal breaks in the 2-minute R-R data segments, a new segment was started immediately after a break to minimize loss of data. The R-R interval data sets were transformed to a continuous digital signal by linear interpolation, and then the event series was resampled at the rate of 16 Hz. The reciprocal of each R-R interval was computed to obtain the respective instantaneous heart-rate reading. Fast-Fourier-Transformed power spectra were then computed for the FHR signal segments (MATLAB®-oriented tailor-made signal-analysis program, MARAPS, Tampere, Finland) (15) .

The FHR variability spectrum in a 2-minute R-R data segment was integrated over the total frequency band (0.04 – 1.0 Hz), as well as over the low-frequency (LF) band from 0.04 Hz to 0.15 Hz (from 2.4 to 7.8 cycles / min) (corresponding mainly to sympathetic and para-sympathetic control), and over the high-frequency (HF) band from 0.15 Hz to 1.0 Hz (from 7.8 to 60 cycles / min) (corresponding to parasympathetic control) (16). To minimize the effect of FHR on FHR variability, we calculated the coefficient of component variance (square root of power spectra / mean R-R interval)

(17). Low-to-high frequency ratio (LF/HF) was assessed to display the balance of sympathetic and parasympathetic control (16). All the spectral variability data are given in arbitrary units (AU).

Statistical methods. The results were statistically analyzed by SAS System for Windows, release 8.01 (SAS Institute, Cary, North Carolina, USA). The continuous variables in the clinical data were analyzed with a Student's two-sample test or a Wilcoxon two-sample test, as appropriate. The proportion of operative deliveries between groups was compared with a chi-square test. Because of a skewed distribution of data, FHR variability values were square-root-transformed. The results are expressed as mean (range), median [range] or number (percentage %), as appropriate. The associations between spectral bands and FBS pH were analyzed with the Spearman correlation coefficient. Because gestational age is known to affect FHR variability (18) (19), the partial correlation coefficient between spectral bands and the FBS pH was also calculated by adjusting correlation for gestational age as a covariate. The differences of spectral bands between subgroups were tested with the T-test. P –value <0 .05 was considered significant.

Results

Clinical data from the studied fetuses are presented in Table 1. Low-FBSpH -fetuses revealed, as expected, more operative deliveries, and had shorter time lag from FBS to birth.

Fetuses developing intrapartum acidemia (normal first scalp pH-value, or normal CTG, with last scalp pH-value ≤ 7.20) had a more pronounced increase in the spectral powers of FHR variability from the first to second measure points when compared to fetuses with repeatedly normal scalp pH (>7.20) (p=0.0005; Fig.2).

Overall FHR variability was higher in low-FBSpH -fetuses when compared with control fetuses (p=0.038; Fig. 3). However, the subgroup of most-affected fetuses (those with FBS pH ≤ 7.10) had significantly lower FHR variability spectral powers when compared to fetuses with FBS pH 7.11-7.20 (p=0.047; Fig. 3). No differences in LF/HF ratio were found between the study groups (data not shown).

In low-FBSpH -fetuses, overall spectral powers of FHR variability had weak positive correlation with FBS pH (total power; r = 0.29, p=0.008), whereas the correlation was poor and negative in fetuses with FBS >7.20 (total power; r = -0.15, p=0.001). In these groups, LF and HF spectral powers did not correlate any better with FBS pH. However, in fetuses with FBS pH ≤ 7.10 HF, spectral powers of FHR variability correlated (r=0.498; p=0.018) with FBS pH. Adjusting correlations for gestational age had no effect on the results (data not shown).

Discussion

This study shows that in the course of delivery, spectral powers increased both in fetuses with constantly normal FBS and in low-FBSpH -fetuses. However, the increase was more pronounced in low-FBSpH -fetuses. This finding is in accordance with previous ones (20) confirming that fetuses react to normal labor stress by increasing heart rate variability. However, fetuses forced to adapt to increasing demands during delivery seem to react more intensively.

Spectral powers of FHR variability were higher in low-FBSpH -fetuses compared to fetuses with no indications of

intrapartum hypoxia. However, in the subgroup of most-affected fetuses (FBS pH ≤ 7.10), FHR variability was the lowest. Furthermore, FHR variability correlated positively with fetal scalp pH in low-FBSpH -fetuses. This suggests that vagal control diminishes with decreasing pH.

Our results from a large number of deliveries are in agreement with experimental studies, suggesting that in the acute phase of hypoxia without acidemia, the autonomic nervous system is activated, and FHR variability is increased (21). As oxygen deficiency prolongs and hypoxia deepens, FHR variability starts to decrease (22). There are only few clinical studies published on the association of FHR variability as assessed with spectral analysis and birth acidosis (9-11,14,23). All these studies show that fetal acidemia alters FHR variability, but detailed comparison of the results is difficult because of methodological differences. We have previously shown that total, LF and HF FHR variability initially increase, but when approaching delivery, decrease in those fetuses with cord-artery acidosis when compared with fetuses with normal cord-artery pH (9).

The association of FBS pH with FHR variability is largely unknown. Van Laar et al (24) have previously investigated, in a small population, the relation of fetal scalp pH to FHR variability. They found no association of LF (0.04-0.15 Hz) or HF (0.4-1.5 Hz) powers with FBS pH. They also calculated normalized LF (LF divided by total power) and normalized HF powers of FHR variability that were associated with FBS pH. It is notable that their spectral bands were different from ours, and the number of fetuses in their study was too small to enable clinical conclusions. We found that in low-FBSpH -fetuses all spectral powers of FHR variability decreased with decreasing fetal scalp pH. However, the variance in FHR variability is large. This large variance during labor is likely to illustrate dynamic alterations in autonomic nervous system function. Large variation in FHR variability identifies a fetus capable of responding actively to the stress of labor and delivery, even with development of acidemia. This large variation of FHR variability is challenging in the context of clinical application, and no cut-off values for clinical action can be established; spectral analysis of FHR variability may thus be used in a similar fashion to ST analysis -with continuous assessment of intraindividual change in the spectral powers of FHR variability.

The crucial marker for worsening fetal hypoxia is decreased FHR variability, possibly reflecting decreasing autonomic nervous compensation capacity (25). In our study, low-FBSpH -fetuses showed a decrease in all spectral bands of FHR variability as FBS pH decreased. Furthermore, the lowest FHR variability was detected in fetuses with FBS pH ≤ 7.10. This association of spectral bands and FBS pH was most pronounced in HF powers in fetuses with the most marked acidemia suggesting a decrease in vagal activity. Decreased fetal breathing activity due to hypoxia could also lead to decreased FHR variability, although intrapartum fetal breathing is rare and further diminished by hypoxia (26). Decreased FHR variability near delivery may thus be a sign of an alteration in the pattern of fetal reactions to oxygen deficiency (27).

From the methodological point of view, FHR variability data is easily and continuously obtained simultaneously with the fetal ECG during delivery. Therefore, possible changes can be promptly analyzed. However, spectral

analysis of FHR variability requires a stationary signal, and for calculation of LF variability, a continuous signal segment of at least 75 seconds is needed (28). This is a shortcoming in the current data, because during delivery, the FHR is often non-stationary, with large fluctuations due to uterine and fetal activity. We studied FHR variability in 2-minute signal segments, thus contractions are unlikely to contribute to our results, as they should take place at least three times within a 2-minute signal segment in order to be detected by spectral analysis. The standard deviation of each spectral band was quite wide, reflecting dynamic features of FHR variability and suggesting that fetal state interacts with FHR variability changes (9,21).

Could spectral analysis of FHR variability be used in clinical practice? Because of large individual variation in the spectral powers of FHR variability, a single measure cannot be used to determine fetal well-being. The results in this study show that FHR variability changes in line with fetal acid-base balance. Therefore, a possibly useful application of FHR variability analysis could be a follow-up of changes in FHR variability during delivery. Moreover, assessment of spectral analysis of FHR variability may complement other methods of assessing fetal well-being during delivery.

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Ethics approval: Ethical approval was obtained in those centers where STAN® was not being used as part of standard care.

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Table 1. Clinical data of the studied fetuses. Values are expressed as mean (range), median [range] or number (%). p = statistical significance for group difference, FBS = fetal scalp blood sample.

	Low-FBSpH-fetuses (n=81)	**Control fetuses (n=462)**	***p*-value**
Gestational age, weeks	40 [36-42]	40 [36-43] (n=461)	.6*
Birthweight, g	3348 (1850-4350)	3468 (1940-5160) (n=461)	.07**
Operational deliveries, n (%)	73 (90 %)	253 (55 %)	<.0001***
FBS pH	7.14 (6.93-7.20)	7.31 (7.21-7.55)	<.0001**
Cord arterial pH	7.13 (6.89-7.4) (n=75)	7.21 (6.94-7.43) (n=428)	<.0001**
5-minute Apgar score	9[1-10]	10 [3-10]	<.0001*
Timelag from FBS to birth, min	21 [4-142]	84 [5-944]	<.0001*

* Wilcoxon two-sample test

** Two-sample t test

*** Chi-square test

Figure 1. A flow chart on the process of selection of the studied fetuses. ECG = electrocardiogram, FBS = fetal scalp blood sample.

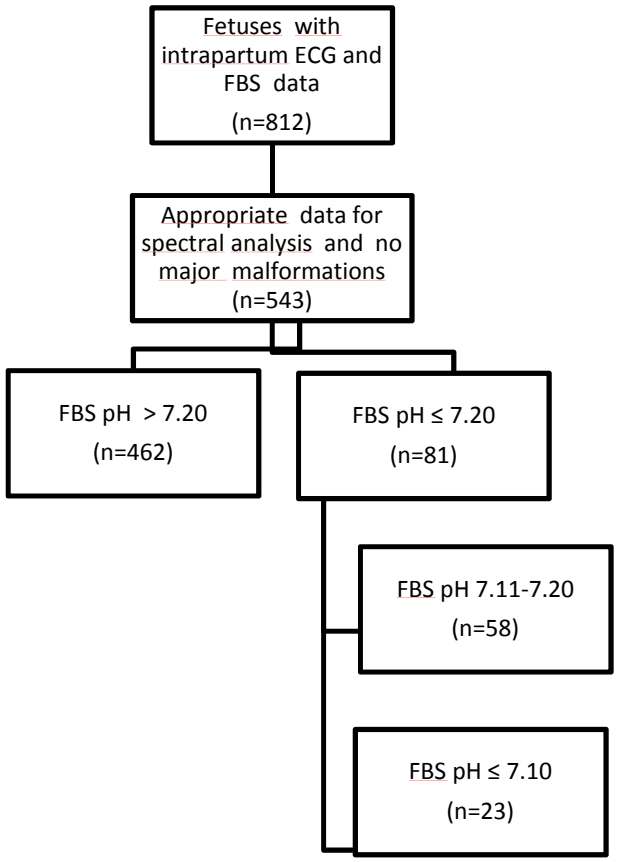


Figure 2. Change in the spectral powers of fetal heart rate (FHR) variability in the course of delivery in control fetuses with stable FBS pH > 7.20 vs. fetuses with developing hypoxia with low FBS pH (≤ 7.20).
Spectral powers of FHR variability are measured before normal first FBS pH or during normal CTG (baseline), and before last FBS pH (last FBS). The spectral power of FHR variability is presented in arbitrary units (AU).

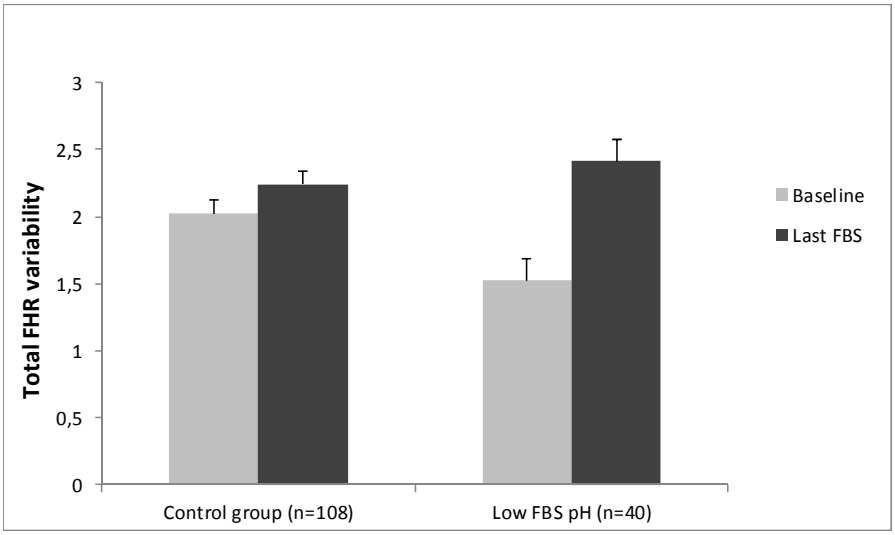
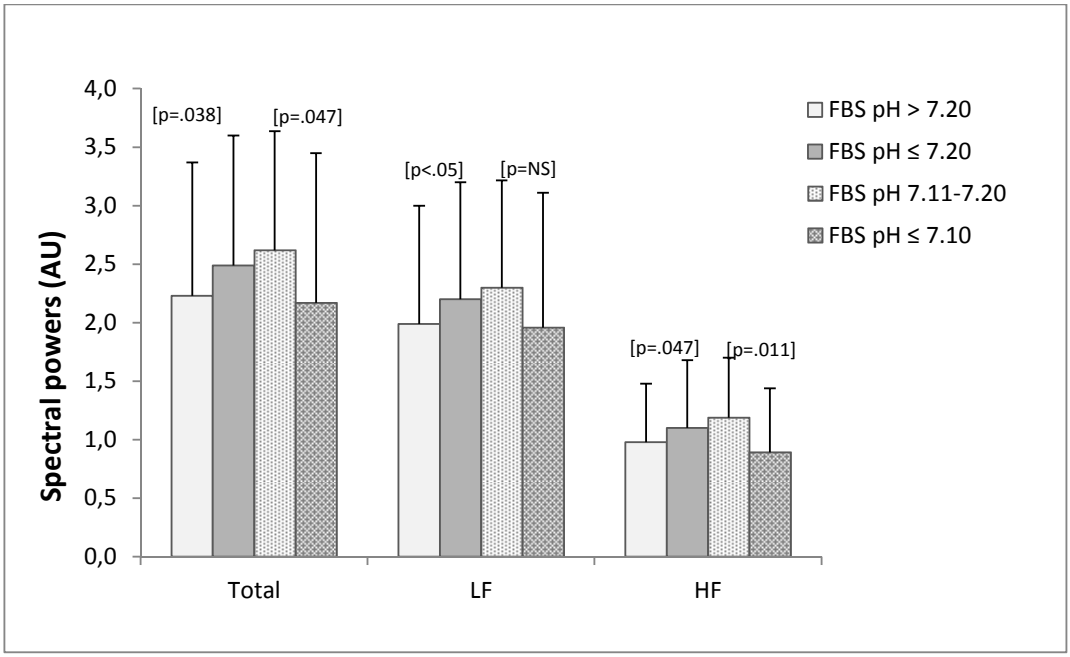


Figure 3. Total, low-frequency (LF) and high-frequency (HF) spectral powers of fetal heart rate (FHR) variability in control fetuses (fetal scalp blood sample (FBS) pH > 7.20) and in low-FBSpH-fetuses (FBS pH ≤ 7.20). Also, the subgroups with FBS pH 7.11-7.20 and FBS pH ≤ 7.10 are presented separately. *p*-values are presented between the controls and low-FBSpH-fetuses and between the subgroups. Mean values are in arbitrary units (AU).



References

(1) Alfirevic Z, Devane D, Gyte GM. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. Cochrane Database Syst Rev 2006;3.

(2) NICE Clinical Guideline 2007. Intrapartum care. Care of healthy women and their babies during childbirth. .

(3) Sabir H, Stannigel H, Schwarz A, Hoehn T. Perinatal hemorrhagic shock after fetal scalp blood sampling. Obstet Gynecol 2010 Feb;115(2 Pt 2):419-420.

(4) Schaap TP, Moormann KA, Becker JH, Westerhuis ME, Evers A, Brouwers HA, et al. Cerebrospinal fluid leakage, an uncommon complication of fetal blood sampling: a case report and review of the literature. Obstet Gynecol Surv 2011 Jan;66(1):42-46.

(5) Chauhan SP, Klauser CK, Woodring TC, Sanderson M, Magann EF, Morrison JC. Intrapartum nonreassuring fetal heart rate tracing and prediction of adverse outcomes: interobserver variability. Am J Obstet Gynecol 2008 Dec;199(6):623.e1-623.e5.

(6) Parer JT, King T, Flanders S, Fox M, Kilpatrick SJ. Fetal acidemia and electronic fetal heart rate patterns: is there evidence of an association? J Matern Fetal Neonatal Med 2006 May;19(5):289-294.

(7) van Ravenswaaij-Arts CM, Kollee LA, Hopman JC, Stoelinga GB, van Geijn HP. Heart rate variability. Ann Intern Med 1993;118(693175795):436-47.

(8) Sibony O, Fouillot JP, Benaoudia M, Benhalla A, Oury JF, Sureau C, et al. Quantification of the fetal heart rate variability by spectral analysis of fetal well-being and fetal distress. Eur J Obstet Gynecol Reprod Biol 1994;54(294350130):103-18.

(9) Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Välimäki IA, Rosén KG, et al. Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. BJOG 2005 Apr;112(4):418-423.

(10) van Laar JO, Peters CH, Vullings R, Houterman S, Bergmans JW, Oei SG. Fetal autonomic response to severe acidaemia during labour. BJOG 2010 Mar;117(4):429-437.

(11) Siira S, Ojala T, Ekholm E, Vahlberg T, Blad S, Rosén KG. Change in heart rate variability in relation to a significant ST-event associates with newborn metabolic acidosis. BJOG 2007 Jul;114(7):819-823.

(12) Luttkus AK, Norén H, Stupin JH, Blad S, Arulkumaran S, Erkkola R, et al. Fetal scalp pH and ST analysis of the fetal ECG as an adjunct to CTG. A multi-center, observational study. J Perinat Med 2004;32(6):486-494.

(13) Wiberg-Itzel E, Lipponer C, Norman M, Herbst A, Prebensen D, Hansson A, et al. Determination of pH or lactate in fetal scalp blood in management of intrapartum fetal distress: randomised controlled multicentre trial. BMJ 2008 Jun 7;336(7656):1284-1287.

(14) Rantonen T, Ekholm E, Siira S, Metsälä T, Leino R, Ekblad U, et al. Periodic spectral components of fetal heart rate variability reflect the changes in cord arterial base deficit values: a preliminary report. Early Hum Dev 2001;60(321066613):233-28.

(15) Välimäki I, Rantonen T. Spectral analysis of heart rate and blood pressure variability. Clin Perinatol 1999 Dec;26(4):967-80, x.

(16) Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93:1043-165.

(17) Hayano J, Sakakibara Y, Yamada M, Kamiya T, Fujinami T, Yokoyama K, et al. Diurnal variations in vagal and sympathetic cardiac control. Am J Physiol 1990;258(3):H642-6.

(18) Assali NS, Brinkman CR,3rd, Woods JR,Jr., Dandavino A, Nuwayhid B. Development of neurohumoral control of fetal, neonatal, and adult cardiovascular functions. Obstet Gynecol 1977;129:748-59.

(19) van Laar JO, Peters CH, Vullings R, Houterman S, Oei SG. Power spectrum analysis of fetal heart rate variability at near term and post term gestation during active sleep and quiet sleep. Early Hum Dev 2009 Dec;85(12):795-798.

(20) Pello LC, Rosevear SK, Dawes GS, Moulden M, Redman CW. Computerized fetal heart rate analysis in labor. Obstet Gynecol 1991 Oct;78(4):602-610.

(21) Westgate JA, Bennet L, Gunn AJ. Fetal heart rate variability changes during brief repeated umbilical cord occlusion in near term fetal sheep. Br J Obstet Gynaecol 1999;106(799355476):664-71.

(22) Dalton KJ, Dawes GS, Patrick JE. Diurnal, respiratory, and other rhythms of fetal heart rate in lambs. Obstet Gynecol 1977;127(477109232):414-24.

(23) Chung DY, Sim YB, Park KT, Yi SH, Shin JC, Kim SP. Spectral analysis of fetal heart rate variability as a predictor of intrapartum fetal distress. Int J Gynaecol Obstet 2001;73:109-116.

(24) van Laar JO, Peters CH, Houterman S, Wijn PF, Kwee A, Oei SG. Normalized spectral power of fetal heart rate variability is associated with fetal scalp blood pH. Early Hum Dev 2011 Apr;87(4):259-263.

(25) Field DR, Parer JT, Auslender R, Baker BW, Ross BK, Leicht CH. Fetal heart rate variability and cerebral oxygen consumption in fetal sheep during asphyxia. Eur J Obstet Gynecol Reprod Biol 1991;42(292111925):145-53.

(26) Boylan P, Lewis PJ. Fetal breathing in labor. Obstet Gynecol 1980;56:35-38.

(27) Assesment of fetal reactivity biopatterns during labour by fetal ECG analysis. ; 2009.

(28) Berntson GG, Bigger JT,Jr, Eckberg DL, Grossman P, Kaufmann PG, Malik M, et al. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 1997 Nov;34(6):623-648.