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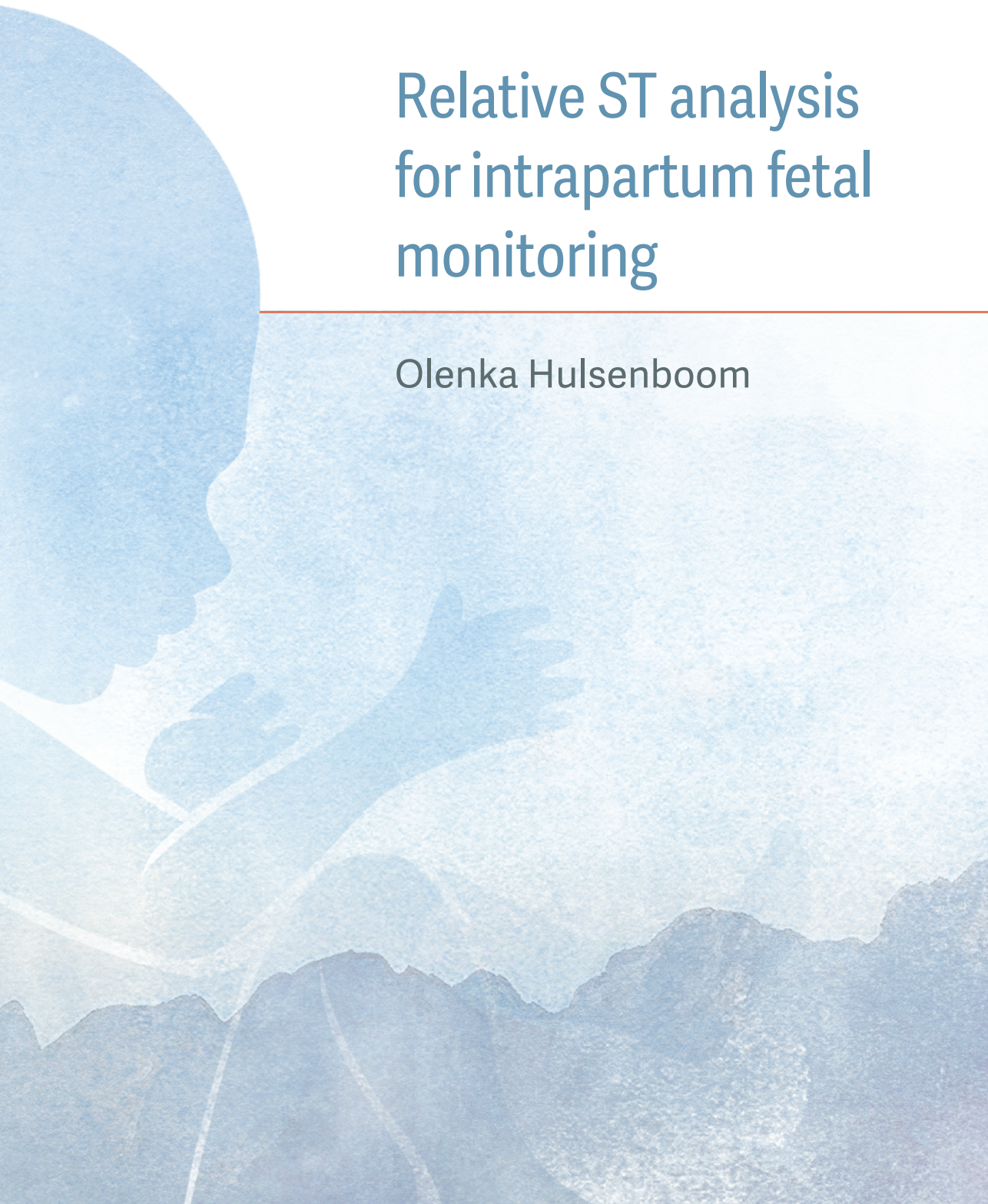
Olenka Hulsenboom



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THESIS

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door

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Het onderzoek dat in dit proefschrift wordt beschreven is uitgevoerd in overeenstemming met de TU/e Gedragscode Wetenschapsbeoefening.

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CHAPTER 1

General introduction and outline of this thesis

The main goal of obstetric health care is to achieve safe pregnancy and childbirth for both mother and child. The World Health Organization estimates that 130 million babies are born around the world every year.[1] Most pregnancies and deliveries are uncomplicated, but every year 6.3 million babies die during pregnancy, delivery or within the first week of life.[1] In high income countries, perinatal death rates are relatively low, but even here 20-30% of these deaths is still preventable.[2]

In the Netherlands 5.1 out of 1000 births result in stillbirth or neonatal death in the first 28 days after birth.[a,3] Four major causes contribute to 85% of perinatal deaths in the Netherlands, the so-called big four: growth restriction, preterm birth, severe congenital anomalies and asphyxia.[3,4] Timely recognition of these conditions may lower both perinatal mortality and morbidity. Therefore, optimal fetal monitoring technologies are crucial for obstetric health care providers to intervene timely when necessary. Different technologies were developed over the years with both benefits and limitations. Due to poor diagnostic accuracy, additional monitoring can lead to unnecessary interventions, without improving maternal and neonatal outcome.

This thesis focuses on fetal electrocardiography (ECG) during labor as a method to monitor fetal well-being. This chapter will provide a brief introduction on fetal physiology, the currently available fetal monitoring technologies and an overview of the questions answered in the following chapters.

Embryology of the fetal heart

The fetal heart is the first organ to function during the development of the human embryo. The main function of the heart is to distribute blood through the blood vessels, so the tissues of the body can exchange oxygen, nutrients and waste products. The embryology of the heart is illustrated in Figure 1. The heart originates from the mesoderm layer: two tubes are formed which fuse to one primitive heart tube. From 3 weeks after fertilization, it starts to beat, forcing the blood to flow from the tail towards the head. Between day 23 and 28 after fertilization, this tube starts to loop and rotate, into a S-shape. From day 28, internal septa start to form, which divide the heart into two atria and two ventricles. The atrioventricular and semilunar valves are formed between day 35 and 63.[5]

a Including stillbirth, perinatal and neonatal death from 24 weeks of gestation until 28 days after birth.

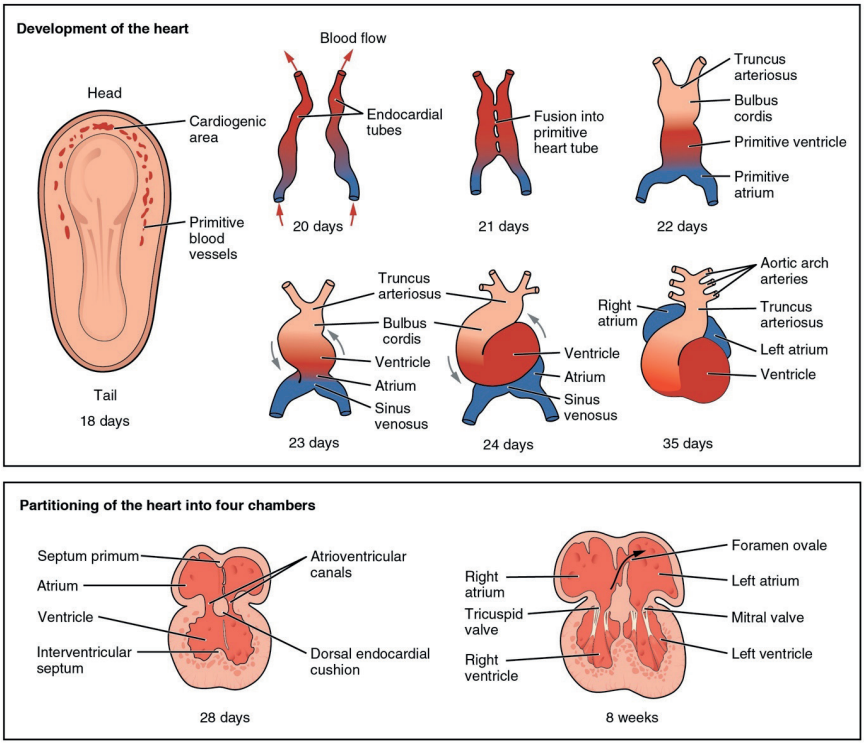

Figure 1. Development of the human heart. The upper panel demonstrates the embryological stages of the formation of the human heart between 18 and 35 days after fertilization. The lower panel demonstrates the embryological formation of the four chambers at 28 days and 8 weeks after fertilization. Adapted from: Anatomy & Physiology.[b]

Fetal circulation

The fetus obtains oxygen from the maternal circulation via the placenta (Figure 2). Oxygenated blood flows through the umbilical vein towards the fetus and enters the fetal circulation through the liver and the ductus venosus into the vena cava inferior. From there it flows into the right half of the fetal heart and mixes with deoxygenated blood from the fetal body. Two shunts (the foramen ovale, between both atria, and the ductus arteriosus, between the aorta and the pulmonary trunk) enable the mixed blood to largely bypass the fetal pulmonary circulation and flow towards the brain and the body. Deoxygenated blood flows through two umbilical arteries back towards the placenta.[6]

b Access for free at https://openstax.org/books/anatomy-and-physiology/pages/19-5-development-of-the-heart

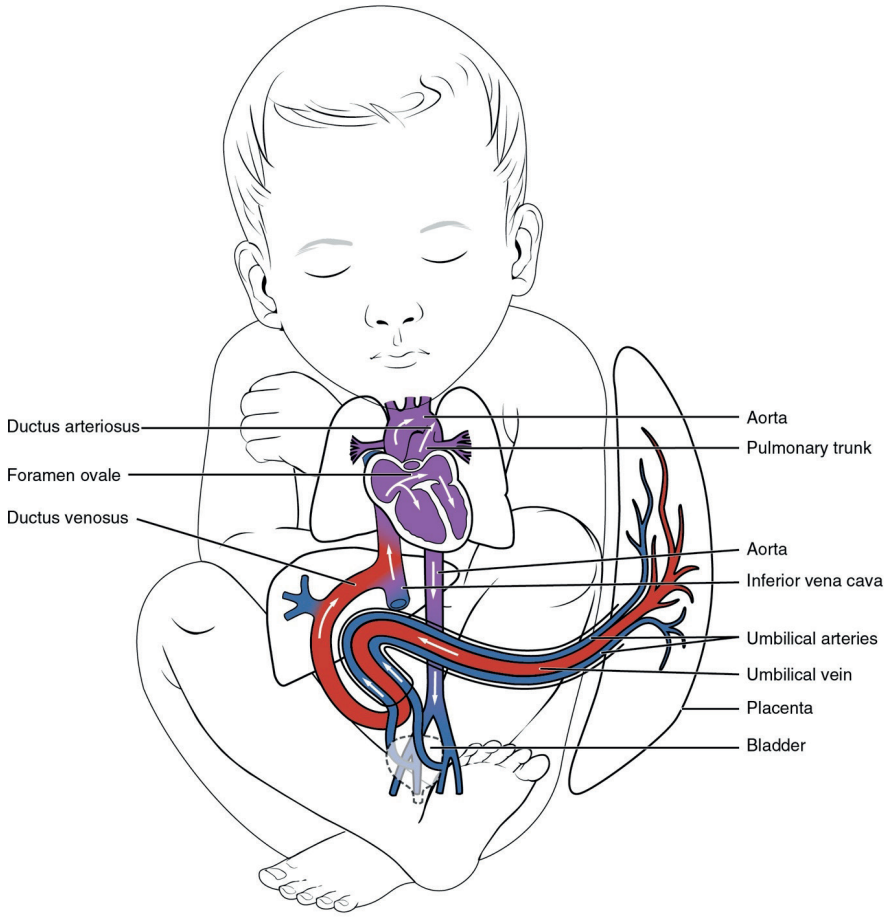

Figure 2. Fetal circulation and shunts. One umbilical vein transports oxygen rich blood from the placenta towards the fetus, two umbilical arteries transport deoxygenated blood in the opposite direction. The fetal circulation has three shunts that allow the blood to be distributed differently compared to the adult circulation. 1. The foramen ovale, situated in the septum between both atria, allows blood to flow from the right into the left atrium. 2. The ductus arteriosus is a connection between the pulmonary trunk and the aorta. These two shunts allow the blood to bypass the not yet functional pulmonary circulation. 3. The ductus venosus is the connection between the umbilical vein and the vena cava inferior. This is the point where oxygen rich blood enters the fetal circulation. Adapted from Anatomy & Physiology.[c]

c Access for free at https://openstax.org/books/anatomy-and-physiology/pages/20-6-development-of-blood-vessels-and-fetal-circulation

After birth, the circulation adapts to the new condition outside the uterus. The first breath fills the lungs with air, which lowers the pressure in the pulmonary circulation, allowing more blood to flow through the lungs towards the left atrium. The increased blood pressure closes the foramen ovale. The ductus arteriosus closes within the first days after birth, due to higher oxygen saturation which causes the smooth muscle cells to contract.[6]

Cardiac conduction and electrocardiography

The heart consists of cardiac muscle cells which can initiate and propagate electrical impulses. The cells can be divided in two types: myocardial contractile cells (99%), that mainly contract and thereby pump the blood through the heart towards the blood vessels, and myocardial conducting cells (1%), that initiate and propagate electrical impulses to trigger contractions.[7]

Electrical impulses initiate from the sinoatrial (SA) node, the pacemaker of the heart, in the upper posterior wall of the right atrium. These electrical impulses propagate through internodal pathways towards the atrioventricular (AV) node, which slows down the propagation. In the meantime, both atria contract and pump blood into both ventricles. From the AV node the electrical impulses are conducted by the bundle of His through the ventricular septum, splitting into two branches and following the Purkinje fibers through both ventricles. This triggers the contraction of the ventricles, which pump the blood into the arteries (Figure 3).[7]

The propagation of electrical impulses through the cardiac tissue forms an electrical current that can be measured at the surface of the human body by electrodes. This technology is called ECG. Two electrodes form one lead and represent the direction of the electrical current between those leads. A positive deflection represents a conduction towards the electrode and a negative deflection represents electrical activity away from the electrode. In adult ECG registration, the standard 12-lead ECG represents a 3D representation of the electrical activity in the heart. Each heart cycle (the conduction of electrical activity and the mechanical contraction during one heart beat) can be divided in different segments that are distinguishable in the ECG (Figure 4): the P-wave represents the depolarization of the atria, the QRS-complex represents the depolarization of the ventricles and the T-wave represents the repolarization of the ventricles. The distance between two consecutive R-peaks (i.e., the RR-interval) represents the time between two heart cycles and can be used to calculate the heart rate.

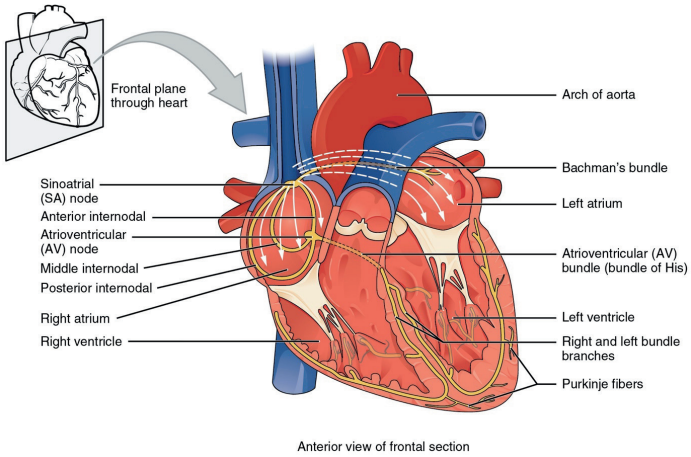

Figure 3. Conduction in the heart. The electrical impulses in the heart are conducted from the sinoatrial node through intranodal pathways throughout the atria towards the atrioventricular node. From there, the bundle of His conducts the impulses through the ventricular septum and splits into the left and right bundle branches. Consecutively, the Purkinje fibers conduct the impulses throughout the ventricles of the heart. Adapted from Anatomy and Physiology.[d]

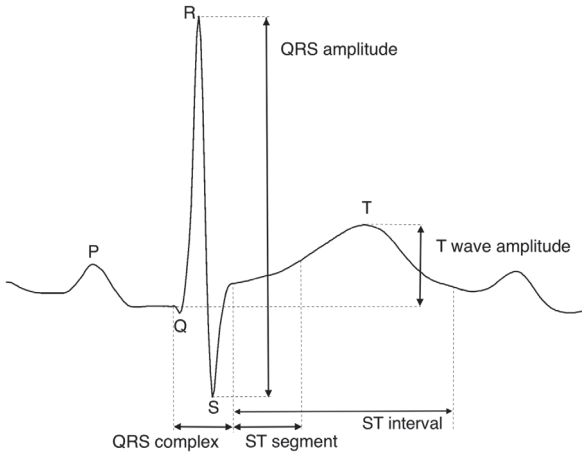

Figure 4. Electrocardiogram parameters. The electrocardiogram presents the electrical activity of the different stages during each cardiac cycle. The P-top represents the depolarization of the atria, the QRS-complex represents the depolarization of the ventricles, the ST segment including the T-top represents the repolarization of the ventricles. The T/QRS ratio is the quotient of the T-wave amplitude and QRS-amplitude. Adapted from Hulsenboom et.al. 2019.[8]

d Access for free at https://openstax.org/books/anatomy-and-physiology/pages/19-2-cardiac-muscle-and-electrical-activity

Adaptations to lower oxygen levels

A fetus depends on the maternal circulation (i.e., maternal oxygenation and maternal blood flow towards the placenta) and placental function to obtain oxygen. Fetal hemoglobin has a higher affinity to bind oxygen and a relatively low blood pressure helps the fetus to ascertain a faster circulation to survive and grow in a situation with lower oxygen saturation (the uterus). A fetus is able to adapt to situations when even less oxygen is available, for example during contractions of the uterus during labor. A lower oxygen level in the fetal circulation can be divided into three levels:

1. Hypoxemia - a lower oxygen saturation in the fetal (arterial) blood. A fetus adapts to hypoxemia by reducing fetal movements and slowing down growth. This way, the fetus reduces its oxygen requirement.
2. Hypoxia - a lower oxygen saturation in the peripheral tissues. A fetus adapts to this condition by releasing stress hormones (adrenalin and noradrenalin). The peripheral resistance increases, which causes a redistribution of blood flow towards the most crucial organs (brain, heart and adrenal glands) and an increased heart rate. Peripheral tissues start with anaerobic metabolization (not requiring oxygen), thereby producing acid waste products (lactate).
3. Asphyxia - a lower oxygen saturation in the central tissues, causing metabolic acidosis and organ failure. A fetus reacts with maximal activation of the sympathetic nervous system and stress hormone release. Cells of the central organs switch to anaerobic metabolization, thereby using the glycogen reserves from the liver and heart muscle cells. Lactate is formed and causes metabolic acidosis in both the organs and peripheral tissues. If this condition continues over minutes, irreversible damage to the fetal brain and heart or even death may occur.[9]

Fetal monitoring technologies

As the fetus is still hidden inside the maternal body, different layers (e.g., amniotic fluid, amnion, chorion, uterus, maternal abdominal muscles, connective tissue and skin) prevent direct measurements of the fetal vital parameters (such as blood pressure). Obstetric health care providers can only detect the fetal heart rate as a source of information to monitor the well-being of the fetus. In advanced labor (after rupture of membranes), the fetal scalp is partially exposed and provides an opportunity to detect the fetal electrocardiogram and perform blood analysis (pH and lactate).

Cardiotocography

Cardiotocography (CTG) is the continuous simultaneous registration of both the fetal heart rate and uterine contractions. Figure 5 shows an example of a CTG registration. CTG was introduced in the 1960s and became a standard method to detect

fetal well-being during labor.[10] The fetal heart rate can be detected in three ways, two are external (non-invasive) and one is internal (invasive). The first external method uses doppler ultrasound to detect movements of the fetal heart during each contraction. It is vulnerable to signal loss and registering the maternal heart instead of the fetal heart rate. The second external method uses electrodes on the maternal abdomen to detect the fetal ECG signal (non-invasive fetal ECG).[11] The internal method uses an invasive electrode on the fetal head (or breech) and can be applied after sufficient dilation of the cervix and after rupture of the membranes. The electrode can detect the fetal ECG, including the RR-interval to calculate the fetal heart rate.[12]

Visual interpretation of patterns in the fetal heart rate are used to monitor the condition of the fetus. Different parameters can indicate fetal compromise: for example, increased or decreased baseline of the fetal heart rate, reduced heart rate variability, decelerations and bradycardia.[12]

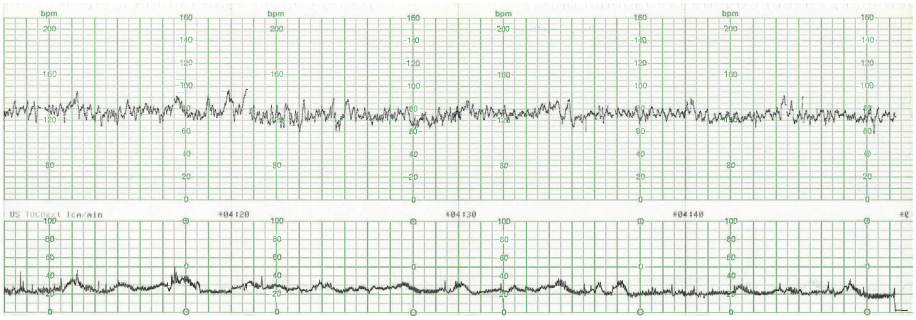

Figure 5. Example of a cardiotocogram during labor. The upper black line represents fetal heart rate, the lower black line represents uterine contractions. Recorded on November 25th 1989, personal archive.

CTG analysis has several limitations. It suffers from substantial intra- and interobserver variability and its specificity is low.[13,14] After introduction of this technology rates of neonatal seizures reduced, but cerebral palsy and infant mortality rates remained equal.[14] False positive interpretation of the CTG leads to unnecessary interventions such as more caesarean sections and instrumental vaginal births.[14] As a result, CTG can be applied as a screening method in clinical practice, but requires additional technologies to prevent unnecessary interventions.

Fetal scalp blood sampling

Fetal scalp blood sampling (FBS) is used as an additional technology in case of an abnormal CTG tracing during labor. The obstetric health care provider collects a few drops of fetal blood from a scratch on the fetal head (or breech), which can be analyzed. Blood pH and/or lactate levels indicate whether metabolic acidosis is present due to asphyxia.[15] Fetal scalp pH obtained shortly before delivery correlates well with the umbilical cord pH directly after birth, therefore it is a useful marker of fetal well-being that can be applied during labor.[16] Limitations of this method are that it can only be obtained after rupture of membranes and with sufficient dilation, that it is invasive, can cause complications (hemorrhage and infection) and that it only provides intermittent information of the fetal condition.

Some studies report that FBS reduces unnecessary interventions in abnormal CTG tracings[17,18], but the evidence is weak. On the contrary, other studies showed that unavailability of FBS is not associated with higher caesarean section rates nor higher neonatal morbidity and mortality.[14,19]

ST analysis (fetal ECG waveform interpretation)

In the 1990s a promising additional technology was introduced: the analysis of the ST segment of the fetal ECG, the so-called ST analysis (STAN method, Neoventa Medical AB, Mölndal, Sweden), acquired by a single scalp electrode.[20]

Animal studies demonstrated a strong correlation between fetal compromise and changes in the fetal ST segment.[21-23] Umbilical cord occlusion resulted in myocardial anaerobic metabolism and showed elevated amplitudes of the ST segment.[21-23] Rosén et. al. showed that prolonged oxygen deprivation was followed by a surge of adrenalin, which induced glycogenolysis. This resulted in an increase of potassium ions in the myocardial cells, which affects the depolarization phase in the heart cycle, represented by an increased T-wave amplitude of the fetal ECG.[24-26]

In ST analysis, T-wave amplitude rises are automatically detected from the fetal ECG by the STAN and processed in three steps into alarms that are made visible to the obstetric health care provider.

1. T/QRS value determination – The T-wave amplitude of a mean ECG complex, obtained by averaging 30 ECG complexes, is normalized against the amplitude of the QRS-complex of the mean ECG complex.
2. T/QRS baseline determination – The median of at least 20 T/QRS values within a 20 minutes window is determined and set as a gauge for future T/QRS values in

the following three hours of the registration. In case a new lower T/QRS baseline is detected, it replaces the old gauge.

3. Alarm generation - New T/QRS values are compared to the T/QRS baseline. In case there is a rise in T/QRS ratio, defined as a difference between T/QRS ratios and the baseline, that exceeds a predefined threshold, an alarm is automatically triggered and reported by the STAN monitor. ST analysis discriminates three types of ST events (alarms): episodic, baseline, and biphasic ST events. Both episodic and baseline events represent an absolute increment of the T/QRS ratio compared to the T/QRS baseline. Episodic events reflect an absolute T/QRS rise compared to T/QRS baseline of at least 0.10, baseline events reflect an absolute T/QRS rise of the instantaneous baseline (determined via the process described in step 2 above) at least 0.05 from the T/QRS baseline gauge. Biphasic ST events are defined as ST intervals with a downward slope.[9]

Whether an alarm generated by the STAN monitor, should be followed by a clinical intervention, depends on the CTG classification by the health care provider. In case the CTG is classified as normal, the alarm is classified as 'non-significant' and can be ignored.[27-29] Non-significant alarms are frequently encountered in clinical practice.[30] In case the CTG is classified as intermediary or abnormal, the alarm might be considered to be significant and a clinical intervention should be prompted.[29]

The clinical value of ST analysis is still under debate. After introduction of the method, it was reported that combined CTG monitoring with ST analysis did significantly lower the rates of metabolic acidosis[31] and operative delivery (cesarean sections and vaginal operative deliveries for fetal distress combined) in two randomized controlled trials.[31,32] However, subsequent multicenter trials, including the most recent American STAN trial, could not reproduce these initial findings[33-36] and meta-analyses showed conflicting results regarding the decrease in metabolic acidosis[37-41].

Outline of this thesis

The following chapters aim to answer the next questions:

- What is the distribution of the fetal electrical heart axis during mid-term pregnancy? (Chapter 2)
- What is the relation between T/QRS baseline value and the diagnostic accuracy of ST analysis? (Chapter 3)

- What is the relation between head orientation and electrode position on scalp ECG waveform? (Chapter 4)
- Can the diagnostic accuracy of ST analysis be improved by relative ST alarms (correcting for initial T/QRS baseline)? (Chapters 5-7)

Chapter 8 provides a general discussion based on the data presented in this thesis. Chapters 9 and 10 provide a summary of this thesis respectively in English and Dutch.

Chapters 2 to 7 have been published and are therefore written to be self-contained. This causes some overlap between chapters.

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CHAPTER 2

Orientation of the electrical heart axis in mid-term pregnancy

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Introduction

The unique fetal shunting system causes an increased cardiac muscle mass in the right ventricle.[1] Cardiac currents initiating each contraction are measured from the outside as the electrocardiogram (ECG), the main direction of propagation is referred to as the electrical heart axis. Ventricular depolarization involves the largest cell mass, yielding the largest ECG signal. Therefore, the QRS segment amplitude mainly defines the electrical heart axis. Due to the increased right ventricular mass in fetuses, the electrical heart axis is expected to point toward the right. This has been confirmed in term fetuses during labor and in neonates directly postpartum.[2,3] In contrast, the electrical heart axis of adults points toward the left.[4] However, it is well-known that in both adults and newborns the orientation of the electrical heart axis can vary widely from person to person.[2]

For term fetuses during labor, the orientation of the electrical heart axis has been described by Larks et al. in the 1960s.[3] Their recording techniques are outdated, and they did not take the fetal orientation into account. Despite these shortcomings, they already acknowledged the possibilities of the electrical heart axis to contribute in distinguishing between normal intra-uterine development, congenital heart disease and fetal distress.

The orientation of the fetal electrical heart axis during gestation has never been described. The relevance of the electrical heart axis increased, since fetal ECG is used to study fetal well-being more often. The aim of this study is to determine the direction of the fetal electrical heart axis in mid-term pregnancy.

Materials & methods

We performed a post-hoc analysis on data of two (prospective) studies, both approved by the ethical commission of the Máxima Medical Center.[5] Informed consent was obtained in both studies. Women between 18 and 29 weeks of pregnancy, carrying a singleton fetus were included. Exclusion criteria were maternal age below 18 years, multiple pregnancy, any known fetal congenital anomaly, intra-uterine growth restriction (birth weight <p10 for gestational age) and women receiving medication known to have any cardiac side effects. The absence of severe cardiac malformations was confirmed after birth by review of medical charts.

We conducted a single fetal ECG recording of approximately 30 min with eight adhesive electrodes on the maternal abdomen, placed in a fixed configuration (Figure 1). Recordings were performed using a fetal ECG data acquisition system (Nemo Healthcare BV, The Netherlands) operating at a sampling frequency of 1 kHz. The fetal ECG was obtained and analyzed from the abdominal recordings to yield a vectorcardiogram that is normalized for the fetal orientation via a series of signal processing methods, as depicted in Figure 2 and previously described in other studies.[6-10]

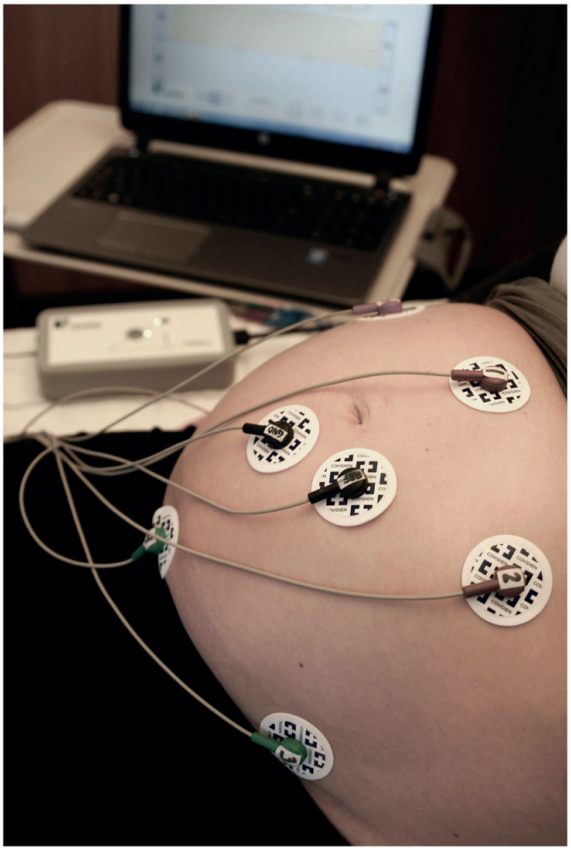

Figure 1. Configuration of the electrodes on the maternal abdomen.

From this normalized fetal vectorcardiogram we obtained the orientation of the electrical heart axis, expressed as degrees ranging from -180° to +180°, as the direction in which the vectorcardiogram has its maximum amplitude. This direction was defined as the average direction of dominant vectors in the QRS complex. These dominant vectors were selected from the point where the R-wave exceeded 70% of

its maximum value for the first time until the point where the R-wave fell below the 70% again.[11] Per fetus, a mean value of the orientation of the electrical heart axis was calculated from the time period of 50 s prior to and 50 s following the ultrasound localization of the fetus in case of good signal quality (at least 80 fetal ECG complexes).

To enable statistical analysis of our results, we categorized the orientations of the electrical heart axis. Both in the frontal and left- sagittal plane we defined 12 categories of possible orientations, the first ranging from 0° to 30°, the second from 30° to 60°, and so on. The mean orientation of the electrical heart axis per fetus is displayed in a histogram. Matlab (The Mathworks, Natick, MA) was used to perform the statistical analysis. Kolmogorov–Smirnov test was used to test whether the distribution of scores was significantly different from a normal distribution. A p-value ≤ 0.05 was considered to be statistically significant.

Results

We included a total of 25 pregnant women between 18 + 1 and 28 + 1 weeks of gestation. Patient characteristics and neonatal outcome are summarized in Table 1. There were no cases of asphyxia or perinatal death. Three pregnancies ended in very preterm labor. Two, at 27 + 2 and 28 + 6 weeks respectively, because of vaginal blood loss due to placenta praevia, and one at 31 + 3 weeks due to spontaneous preterm labor. The interval between the fetal ECG recording and the preterm birth was more than three weeks in all cases.

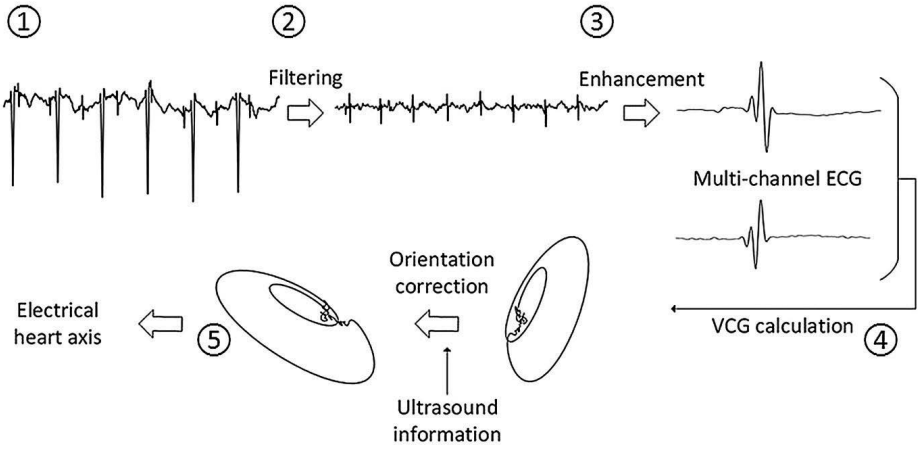

Figure 2. Signal processing steps. From top left, via a clockwise rotation to bottom left;

1. The signal is recorded by the electrodes on the maternal abdomen. Note that the large peaks are maternal QRS complexes, the small peaks that occur approximately twice as frequent as the maternal QRS are the fetal QRS complexes.
2. The signal obtained after filtering the maternal ECG and other interferences. First, interferences such as powerline and (uterine) muscle activity were suppressed by bandpass filtering the recorded signals between 1 and 70 Hz and applying a notch filter that was centered around the powerline frequency. Second, the maternal ECG was suppressed using a technique that dynamically generates a template of the maternal ECG[8] and subsequently subtracts this template from the recorded data. Third, we detected the individual fetal ECG complexes by firstly spatially combining the various recorded channels[9] and subsequently detecting the fetal QRS complexes using a low-complexity R-peak detection method.[7]
3. The fetal ECG is enhanced by averaging the ECG across multiple heartbeats, where the number of heartbeats is dynamically varied by an adaptive Kalman filter and depends on the quality and stationarity of the ECG signal.[6] For every electrode an average ECG signal is determined.
4. Using knowledge on the placement of the electrodes, we calculated the fetal vectorcardiogram by spatial combination of multi-channel fetal ECGs.[10] In case the fetus would change its orientation in the uterus, the vectorcardiogram would rotate with the fetus.
5. Rotated version of the fetal vectorcardiogram. To determine the vectorcardiogram in the fetal frame of reference, similarly as an adult vectorcardiogram would be determined, we performed an ultrasound examination to determine the fetal orientation simultaneously with the ECG measurements. The rotated fetal vectorcardiogram represents a standardized view of the fetal vectorcardiogram (i.e. as if it was recorded with electrodes placed directly on the fetal body). From the standardized view, the fetal electrical heart axis is calculated.

Abbreviations: ECG, electrocardiogram; VCG, vectorcardiogram

Table 1. Characteristics of the study population.

Variable			n
Maternal age (years)	30	±4.5	25
BMI (kg/m²)	24.7	±4.7	25
Nulliparous (n)	18	(72%)	25
GA at measurement (weeks)	24.1	(22.3 - 24.5)	25
GA at delivery (weeks)	39.3	(37.6 - 40.9)	25
Birthweight (g)	3285	(2950 - 3730)	25
Sex (n male)	16	(64%)	25
Apgar Score at 1 minute	9	(9-9)	25
Apgar Score at 5 minutes	10	(10-10)	25
Cord artery pH	7.27	(7.21-7.29)	23
Cord vene pH	7.33	±0.07	17
Metabolic acidosis (n)	0	(0%)	25

Data is presented as mean with standard deviation (±), median with interquartile range (Q1–Q3), or number with percentage (%).
Abbreviations: BMI, Body Mass Index; GA, Gestational Age; n, number.

Figure 3 presents the observed orientation of the fetal electrical heart axis, which shows a considerable amount of variation. In the frontal view, the heart axis points toward the right in most cases. In the left-sagittal view, the heart axis points toward the back in most cases. The orientation of the electrical heart axis in the frontal view varied significantly from a normal distribution; p = 0.016, Kolmogorov–Smirnov test. In the sagittal view, the orientation of the electrical heart axis did not differ significantly from a normal distribution (p = 0.22, Kolmogorov–Smirnov test).

Comment

Although our study population is relatively small, the results are in line with our hypothesis that the fetal heart axis points toward the right due to the increased mass of the right ventricle. In term fetuses during labor, the main direction of the fetal heart axis is to the right (between +100° and +160°).[12] In neonates directly postpartum, the QRS-axis in the frontal view varies between +60° and +160° and the vectorcardiogram points mainly to the right-inferior-anterior direction.[2,13,14] As the mass of the left ventricle increases with age, the orientation of the electrical heart axis gradually deviates toward the left. At the age of one year, the electrical heart axis points to the left (between +10° and +100°).[13] Normal values in adults vary be-

tween -30° and +90°.[4] This all indicates that there is a shifting continuum between the orientation of the electrical heart axis in fetal, neonatal and adult life.

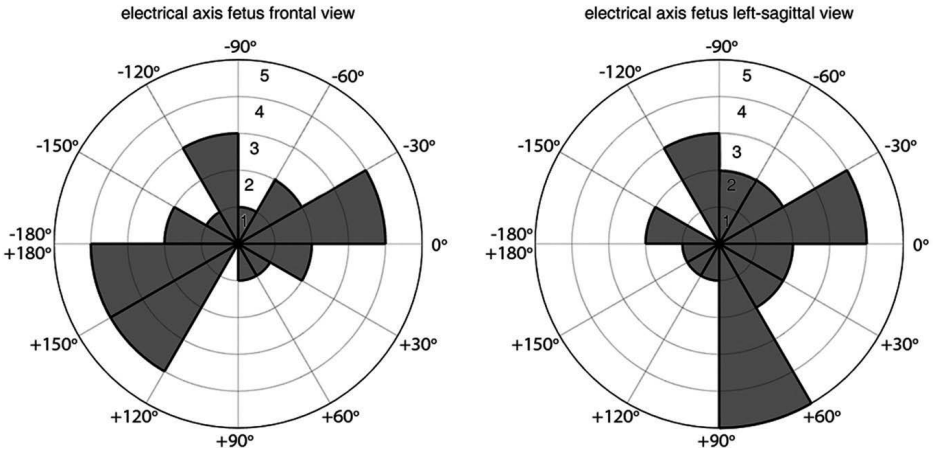

Figure 3. Histograms of the orientation of the electrical heart axis in 25 healthy fetuses. For every fetus, the orientation of the electrical heart axis was determined in both the frontal plane (left histogram) and left-sagittal plane (right histogram). This orientation was subsequently scored in the corresponding histogram, which were defined by dividing all possible orientations, which range between -180° and +180°, in 12 bins of each 30° width. The number of counts per bin are displayed by means of the grey areas in the histogram plots.

In addition, the distribution of orientations of the electrical heart axis in Figure 3 shows that during mid-term pregnancy this orientation varies as much as it does in newborns and in adults. Because the electrical heart axis determines the fetal ECG waveform, it is extremely important for fetal ECG interpretation that the electrical heart axis is taken into account. Alternative direction of the main fetal electrical heart axis has direct consequences for the fetal ECG.

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CHAPTER 3

The electrical heart axis and ST events in fetal monitoring: A post-hoc analysis following a multicentre randomised controlled trial

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Abstract

Objective

Reducing perinatal morbidity and mortality is one of the major challenges in modern health care. Analysing the ST segment of the fetal electrocardiogram was thought to be the breakthrough in fetal monitoring during labour. However, its implementation in clinical practice yields many false alarms and ST monitoring is highly dependent on cardiotocogram assessment, limiting its value for the prediction of fetal distress during labour. This study aims to evaluate the relation between physiological variations in the orientation of the fetal electrical heart axis and the occurrence of ST events.

Methods

A post-hoc analysis was performed following a multicentre randomised controlled trial, including 1097 patients from two participating centres. All women were monitored with ST analysis during labour. Cases of fetal metabolic acidosis, poor signal quality, missing blood gas analysis, and congenital heart disease were excluded. The orientation of the fetal electrical heart axis affects the height of the initial T/QRS baseline, and therefore the incidence of ST events. We grouped tracings with the same initial baseline T/QRS value. We depicted the number of ST events as a function of the initial baseline T/QRS value with a linear regression model.

Results

A significant increment of ST events was observed with increasing height of the initial T/QRS baseline, irrespective of the fetal condition; correlation coefficient 0.63, $p < 0.001$. The most frequent T/QRS baseline is 0.12.

Conclusion

The orientation of the fetal electrical heart axis and accordingly the height of the initial T/QRS baseline should be taken into account in fetal monitoring with ST analysis.

Introduction

Fetal asphyxia is associated with severe perinatal morbidity and mortality. The cardiotocogram, a simultaneous recording of the fetal heart rate and uterine contractions, is used worldwide for fetal surveillance. However, the poor specificity of this method has resulted in increased rates of operative deliveries without a decrease in perinatal mortality or cerebral palsy.[1] ST analysis (STAN) was introduced in 1992 as a promising technique that analyses the ST segment of the fetal electrocardiogram (ECG), acquired using an invasive scalp electrode.[2] ST analysis combined with cardiotocography was reported to significantly lower the rates of metabolic acidosis[3] and operative delivery in two randomised controlled trials.[3,4] However, subsequent multicentre trials, including the recently published large American STAN trial, could not reproduce these initial findings.[5-9] Recent meta-analyses show conflicting results regarding the decrease in metabolic acidosis, which indicates the need for more research.[8,10-13] Meanwhile, Kwee et al.[14] reported that the STAN monitor gives as many ST events in cases of proven uncompromised fetal condition as in situations with deteriorating fetal condition. This is countered by the STAN guidelines that state that ST events must be ignored when cardiotocography shows a reassuring pattern. However, the high inter-observer variability in cardiotocogram interpretation makes this a highly unsatisfying strategy.[15] The correct interpretation of a method as subjective as the cardiotocogram determines whether or not to ignore the ST event or to act upon the alarm, making the success of ST monitoring totally dependent on cardiotocogram assessment.

Background information and hypothesis

Prior to the introduction of ST analysis, the diagnostic value of the fetal ST segment was clearly demonstrated in animal studies.[16-18] Sustained deprivation of oxygen is followed by a surge of adrenalin to induce glycogenolysis, which is accompanied by an increase of potassium ions in the myocardial cells.[19] These potassium ions mainly affect the relaxation phase of the cardiac cycle and lead to an increase in the T-wave amplitude of the fetal ECG.[20]

STAN uses this hypoxia-related rise in T-wave amplitude in a three-step protocol.

1. The T-wave amplitude is normalised against the amplitude of the QRS-complex (mean of 30 ECG complexes), yielding a T/QRS value.
2. A baseline T/QRS value is determined (median of at least 20 T/QRS values within 20 minutes) to gauge future T/QRS values.
3. New T/QRS values are compared to the baseline.

In case a T/QRS value exceeds the baseline by 0.05, a baseline ST event is reported. Smaller exceedings of the baseline can be due to normal beat-to-beat fluctuation in the behaviour of the heart, which is unrelated to the fetal condition. With regard to the detection of rises in T-wave amplitude due to oxygen deprivation, this alarm protocol seems plausible.

The ECG recorded from the fetal scalp electrode is a one-dimensional presentation of the electrical activity of the heart. However, the propagation of electrical currents over the cardiac muscle occurs in all three spatial dimensions. The main direction of this propagation is referred to as the electrical axis of the heart. The orientation of the electrical heart axis with respect to the fetal scalp electrode hence affects the shape and amplitude of the recorded ECG. Similarly, (adult) ECG signals recorded at different locations yield different shapes and amplitudes, as already demonstrated many years ago.[21]

It is known that the orientation of the fetal electrical heart axis can vary between +100 and +160 degrees in mid-term fetuses[22] and between +90 and +180 degrees in term fetuses during labour.[23] Similar inter-person variation in the orientation of the electrical heart axis is present in neonates and adults.[24-27] The STAN monitor attempts to correct for the orientation of the electrical heart axis with the first step in its protocol (normalisation). However, the propagation of the electrical currents during the contraction (QRS) phase of the cardiac cycle has a different orientation than during the relaxation (T) phase. Consequently, normalisation cannot fully compensate for inter-patient differences in the orientation of the electrical heart axis. As a result, fetuses for whom the scalp lead is almost perpendicular to the direction of propagation in the relaxation phase have a very small T-wave amplitude, and typically also low T/QRS values and T/QRS baseline. Similarly, fetuses for whom the electrical heart axis is oriented in a manner creating a propagation during relaxation almost aligned with the scalp lead, typically have a high T/QRS value and T/QRS baseline.

When the hypoxia-induced release of potassium ions affects the electrical current in the relaxation phase in the fetuses with a low T/QRS baseline value, the absolute effect in T-wave amplitude will only be marginal as we look at it from an almost perpendicular direction. In fetuses with high T/QRS values, the rise in T-wave amplitude will be relatively large. Based on this, we hypothesise that normal fluctuations in the electrophysiological behaviour of the heart can stay below the 0.05 threshold, in case the scalp lead is oriented more perpendicular to the relaxation currents. Similarly, the hypoxia-related fluctuations in the electrical behaviour can more easily exceed the 0.05 threshold, when the alignment between the electrical heart axis

and scalp lead is axial. We explain this phenomenon in Figure 1. Previously, Becker et al.[28] described that the initial T/QRS baseline is not related to the fetal condition. The incidence of ST events was stated to be related to the fetal condition[3], and therefore not related to the baseline. This is in contrast with our hypothesis that the STAN monitor will raise fewer ST events for fetuses with a low baseline, and more ST events for fetuses with a high T/QRS baseline.

This paper aims to explain how false ST events can occur, based on normal variations in human physiology. Based on this explanation, clinicians might be able to make a better informed decision whether or not to act upon a ST event in case of inconclusive cardiotocogram assessment.

Materials and methods

We performed a post-hoc analysis with data derived from a large multicentre randomised controlled trial, the Dutch STAN trial.[7] The initial study was approved by the Institutional Review Board of the University Medical Centre Utrecht and was performed between January 2006 and July 2008. After written informed consent, women were randomised to the index group with ST monitoring (STAN S21 or S31 fetal heart monitor) or to the control group, using a conventional fetal heart rate monitor (cardiotocography). The randomisation was performed on a 1:1 basis, web-based with stratification for centre and parity. Since the trial was pragmatic in nature, there was no blinding of patients or caregivers. All gynaecologists, residents and midwives in the participating centres were trained and certified as STAN-users, and decisions were made following the STAN clinical guidelines. Fetal blood sampling was allowed, yet restricted to specific scenarios in the index group. Inclusion criteria were maternal age over 18 years, singleton pregnancy, cephalic presentation, gestational age beyond 36 weeks and an indication for internal electronic fetal monitoring. The included women were assigned to a "high-risk pregnancy" group, since they all received secondary care. In the Netherlands, "low-risk pregnancies" are monitored by midwives or general practitioners (primary care). In both groups, the umbilical cord was double clamped immediately after birth, in order to sample both arterial and venous cord blood.

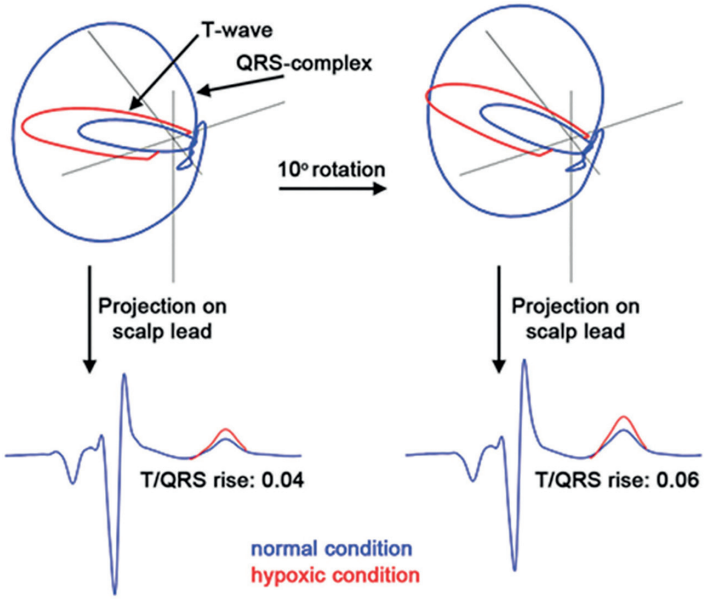

Figure 1. The fetal vectorcardiogram for different orientations of the electrical heart axis. In the top panels, the electrical currents within the heart during a cardiac cycle are depicted in terms of their vectorcardiogram; ventricular contraction (QRS-complex = large loop), relaxation phase (T-waves = small loop). From left to right, the entire vectorcardiogram has been rotated over 10 degrees to simulate a different orientation of the electrical heart axis. Note that these vectorcardiograms are 3-dimensional images and the 10 degree rotation was performed in 3-dimensional space. In the bottom panels, the fetal scalp ECG has been calculated by projecting the vectorcardiograms onto the scalp lead. Before rotation, the baseline T/QRS is 0.05 and the T/QRS rise resulting from hypoxia is 0.04, yielding no ST event. After rotation, the baseline T/QRS is 0.09 and the T/QRS rise resulting from the same level of hypoxia is 0.06, yielding a ST event.

For this post-hoc analysis, we included data from two tertiary hospitals: the University Medical Centre Utrecht and the Máxima Medical Centre Veldhoven, both participating in the multicentre randomised controlled trial. Anonymised information from the initial database was used for this analysis. Following consultation of the Medical Ethical Department in the Máxima Medical Centre, no separate ethical approval was warranted for this study. We only included patients from the index group (with ST monitoring). We excluded patients in whom no STAN registration was performed or no T/QRS baseline value could be determined, cases of metabolic acidosis, cases in which no blood gas analysis was performed postpartum and registrations performed in fetuses with congenital heart disease. Metabolic acidosis was defined as umbilical cord artery blood pH <7.05 and base deficit of the extracellular fluid compartment >12 mmol/l in two blood samples with a minimal pH difference of 0.03. In cases of

only one blood sample or smaller differences between samples, metabolic acidosis was set as cord blood pH <7.10 and base deficit of extracellular fluid >12 mmol/l.

The initial baseline T/QRS value was determined the same way as done in the STAN monitor; as the median of all T/QRS values recorded within the first 20-minute window of the recording, that contained a minimum of 20 T/QRS values. We counted the incidence of ST events throughout the entire registration. Patients were excluded in case a STAN registration was temporarily stopped and more than one STAN file was stored for the patient. For each initial baseline T/QRS value encountered in our data set, we counted the number of patients with that particular baseline. We grouped women with the same initial baseline T/QRS value. Hereafter, we calculated the relative incidence of ST events (defined as the number of ST events per 1000 T/QRS values) as a function of the initial baseline value.

Additionally, we calculated the mean pH and mean base deficit of the extracellular fluid for all women with the same initial baseline T/QRS value. Even though our dataset entails a subset of the data used by Becker et al.[28], it needs to be confirmed that the conclusions from this study, that the height of the initial baseline is not related to fetal outcome, apply to our dataset as well.

Matlab (The Mathworks, Natick, MA) was used to perform the statistical analysis. For analysis of the baseline characteristics, mean, median, standard deviation and interquartile ranges were calculated using IBM SPSS statistics 22.0 for Mac (IBM corp. Armonk, NY, USA). A linear regression model was used to calculate the correlation coefficient for the relation between the number of ST events and the baseline T/QRS value.

Results and discussion

Initially, 1401 patients were screened; in 273 cases ST information was missing, more than one STAN file was available for the same patient, or no T/QRS baseline value had been determined due to short duration of the measurement or poor quality of the data. These cases were therefore excluded. In addition, we excluded 11 cases of fetal metabolic acidosis. Further, no blood sample was available in 12 patients, whom were therefore excluded. In addition, 6 women gave birth to neonates with congenital heart disease, 1 labouring woman younger than 18 years and 1 prior to 36 weeks of gestation during labour were excluded. Eventually, we analysed the

number of ST events in 1097 women. In this group, a total of 1.027.054 T/QRS ratios and 2066 ST events were reported.

The baseline characteristics of the included women are summarised in Table 1.

Table 1. Baseline characteristics of the included patients.

Variable		
Centre UMCU (%)	47.4	
Centre MMC (%)	52.6	
Maternal age (years; mean, [SD])	31.9	[4.6]
Nulliparous (%)	53.4	
Gestational age at delivery (weeks; mean, [SD])	40+0	[1+3]
Spontaneous onset of labour (%)	65.4	
Induction (%)	34.6	
Fetal blood sampling (%)	10.4	
Spontaneous delivery (%)	77.6	
Operative vaginal delivery (%)	10.1	
Caesarean section (%)	12.3	
Apgar score 1' (median, [IQR])	9	[1]
Apgar score 5' (median, [IQR])	10	[0]
pH arterial (mean, [SD])	7.22	[0.07]
Base deficit arterial (median, [IQR])	6	[4]
Birth weight (gram; mean, [SD])	3562	[509]
NICU admission (%)	1.7	
Medium care admission (%)	13.8	
Perinatal mortality (%)	0	

Abbreviations: UMCU; University Medical Centre Utrecht, MMC; Maxima Medical Centre, SD; standard deviation, IQR; interquartile range.

Figure 2 shows the distribution of patients across the various initial baseline T/QRS ratios. In Figure 3, we present the number of ST events as a function of the initial baseline T/QRS value. The results show an average increment of 1.42 ST events per 1000 T/QRS values for a rise of 0.1 of the initial baseline T/QRS. The correlation coefficient between data points and fit was 0.63 ($p < 0.001$), as calculated with the linear regression model.

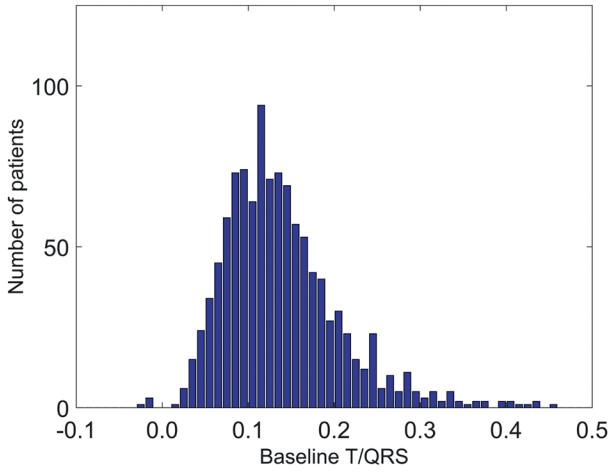

Figure 2. Distribution of patient across the baseline T/QRS values. For each initial baseline T/QRS value encountered in our data set, we counted the number of patients with that particular baseline, showing a non-symmetric distribution with the most frequent encountered baseline T/QRS ratio at 0.12.

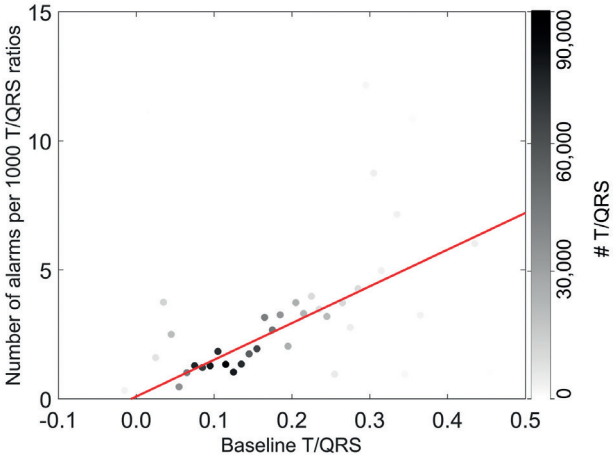

Figure 3. The number of ST events per 1000 T/QRS values as a function of the initial baseline T/QRS value. Cases with the same initial baseline T/QRS were grouped. The intensity of the black colour of the data points relates to the total number of T/QRS ratios that occurred in the group (right column in the graph). The red line represents a linear fit through the data points. There is an average increment of 1.42 ST events per 1000 T/QRS values for a rise of 0.1 of the initial baseline T/QRS. The correlation coefficient between data points and fit was 0.63 ($p < 0.001$), as calculated with the linear regression model.

In Figure 4, we present the pH of the arterial cord blood and base deficit of the extracellular fluid as a function of the initial baseline T/QRS value. The results show no dependency between pH and base deficit on the one hand, and height of the initial baseline on the other hand. The non-significant correlation coefficient between pH and initial baseline height and between base deficit and baseline height was -0.04 (p = 0.14) and 0.03 (p = 0.34), respectively. These results are in line with the results of Becker et al.[28]

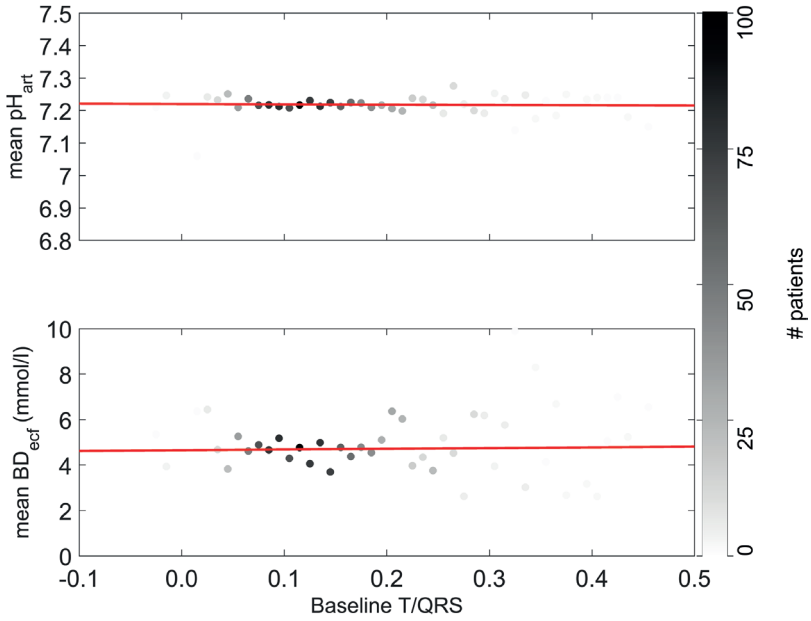

Figure 4. The pH of arterial cord blood and base deficit of the extracellular fluid as a function of the initial baseline T/QRS value. Cases with the same initial baseline T/QRS value were grouped. The intensity of the black colour of the data points relates to the total number of patients that were represented in the group (right column in the graph). The red line represents a linear fit through the data points. The fit suggests a reduction in the pH of 0.0009 and an increase in the base deficit of 0.03 for a rise in 0.1 of the initial baseline T/QRS. The respective correlation coefficients between data points and fit are -0.04 (p = 0.14) and 0.03 (p = 0.34), as calculated with the linear regression model. Abbreviations: BD_{ecf} = base deficit in the extracellular fluid, pH_{art} = pH of the arterial cord blood.

This study suggests that variations in the orientation of the fetal electrical heart axis affect the height of the initial T/QRS baseline and that the height of this baseline determines the occurrence of ST events. This finding could explain for the false ST events that are experienced in everyday clinical practice.

Our aim was to demonstrate that ST events can occur due to normal variations in human physiology (due to variation in electrical fetal heart axis). Therefore, we chose to exclude all cases of metabolic acidosis in this post-hoc analysis. The ST events included in our study, were therefore not related to fetal distress.

The distribution of initial T/QRS baseline values in Figure 2 shows that relatively high baselines are encountered more often than low baselines. Since high baselines are hypothesised to lead to false positive ST events (i.e. alarms while good fetal condition) and low baselines are hypothesised to lead to false negative ST events (i.e. no alarms while compromised fetal condition), this distribution of baseline values can explain why more false positive than false negative ST events are encountered in clinical practice. Since higher baselines do not relate to higher incidences of fetal distress (see Figure 4 and Becker et al.[28]) and considering the large patient population we analysed, we conclude that the presented results support our hypothesis. In other words, some fetuses have a relatively high probability of getting ST events and some fetuses have a relatively low probability, irrespective of their condition. Whether the relatively low probability of getting ST events in case of low initial T/QRS baseline indeed leads to more false negative ST events needs to be confirmed on a dataset including more cases of metabolic acidosis.

In addition, we propose that ST events are unreliable in case of high or low baseline T/QRS values. In case of an average T/QRS baseline value, the incidence of false ST events will be lower. When using the STAN monitor in clinical practice, clinicians should be aware of this limitation. In case of inconclusive cardiotocogram assessment in combination with a high or low baseline T/QRS, fetal blood sampling can be used for complementary diagnostic information. However, the additional value of fetal blood sampling is uncertain and repeated fetal blood sampling is an independent risk factor for caesarean delivery.[29] In case of average baseline T/QRS, ST events can be considered more reliable and could be considered as complementary diagnostic information. ST analysis based on relative elevations of the T/QRS ratio with respect to the baseline or standardised non-invasive fetal ECG recordings[30] might be feasible solutions, that warrant further research. In addition, the relation between signal quality and T/QRS reliability needs to be explored in future research, including analysis of the effects of signal quality of small variations in the ECG that are caused by e.g. rotation of the fetal head at the end of labour.

Conclusions

This study showed a significant increment of ST events with increasing height of the initial T/QRS baseline; correlation coefficient 0.63, $p < 0.001$. The orientation of the fetal electrical heart axis affects the height of the T/QRS baseline, and therefore the incidence of ST events. This should be taken into account in fetal monitoring with ST analysis.

Acknowledgements

We would like to thank Professor K.G. Rosén for his valuable input.

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CHAPTER 4

Head orientation and electrode placement potentially influence fetal scalp ECG waveform

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Abstract

Background

Fetal monitoring based on electrocardiographic (ECG) morphology is obtained from a single unipolar fetal scalp electrode. Ideally, it should be obtained from multiple leads, as ECG waveform depends on alignment between electrode and electrical heart axis. This alignment is unknown in fetuses. Besides, fetuses are surrounded by conductive media, which may influence ECG waveform. We explored the influence of electrode position and head orientation on ECG waveforms of unipolar and bipolar scalp ECGs recorded in air and in conductive medium.

Methods

We recorded ECGs in one adult subject at five different scalp positions in five different head orientations both in dry and immersed conditions. The ratio between T-amplitude and QRS-amplitude (T/QRS ratio) of unipolar and bipolar scalp ECGs was determined and compared between all conditions.

Results

In the dry condition, we observed in the unipolar leads little to no difference between different electrode positions (maximal T/QRS difference 0.00–0.01) and minor differences between head orientations (0.02–0.03), whereas bipolar leads showed no recognizable ECG signal at all. During the immersed condition, we found variation in the unipolar leads, both between electrode positions (maximal T/QRS difference 0.02–0.05) and between head orientations (0.03–0.06). Bipolar leads showed different ECG signals in contrasting head orientations.

Conclusions

Both unipolar and bipolar scalp lead-derived ECG waveforms are influenced by electrode position and head orientation when the subject is submerged in a conductive medium. Fetal monitoring based on single scalp lead ECG waveform might be suboptimal, as it lacks correction for fetal head orientation and electrode position.

Introduction

Monitoring of the fetal condition during labor remains a great challenge in obstetric care. Information about the fetal condition can be obtained from the fetal electrocardiogram (ECG) because it provides both fetal heart rate and ECG morphology. The diagnostic value of the ECG morphology analysis to monitor the fetal condition was first demonstrated in animal studies, in which it was shown that the ST-segment changes under influence of oxygen deficiency.[1,2] Nowadays, ST–analysis (STAN®, Neoventa Medical AB, Mölndal, Sweden) is available in clinical practice, where the ECG is measured from a single unipolar fetal scalp electrode.[3]

Combined information from multiple leads is essential to correctly interpret ECG waveform. Amplitudes of the ECG waveform differ between different leads, since the alignment of the different electrodes and the electrical heart axis differs. During fetal ECG measurement in labor, only a single unipolar lead is used. Correct interpretation of the waveform is difficult, as the orientation to the electrical heart axis is unknown.[4] Besides, the fetus is surrounded by conductive media such as amniotic fluid and maternal tissue. We hypothesize that these conductive media influence ECG waveform and thereby impair correct interpretation of the signal.

In this study, we examined our hypothesis in an experimental setting. We examined the influence of electrode position and head orientation on the waveform of unipolar and bipolar scalp ECGs when recorded in air or in a conductive medium.

Materials and methods

Study population

In this experimental case-study we included one healthy member of our research team after informed consent. The ECG was recorded from various electrodes positioned on the scalp during different head orientations, both in a dry condition and an immersed condition. The Daily Board of the Medical Ethics Committee Máxima Medisch Centrum reviewed and approved the research proposal. The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Materials and experimental set-up

Nine gold cup electrodes were placed on the participant's skin: two at each shoulder, two at each superior anterior ischiadic spine, and at five positions of the 10/20 system: on the midline between Fp1 and Fp2 (named F0), on Fz, O1, O2, and on the midline between O1 and O2 (named O0) (Figure 1). Figure 1 represents the configuration of the electrodes. An experienced clinical neurophysiology technician placed the cup electrodes with Elefix as an insulator, Ten20 as conductive paste, and colloid for optimal fixation. We measured the lead of the scalp ECG as the difference between one electrode at the scalp and the Wilson Central Terminal (WCT), as recorded from the conventional ECG configuration at the rump.[5] In addition, we measured bipolar leads, by calculating the potential difference between pairs of electrodes on the scalp.

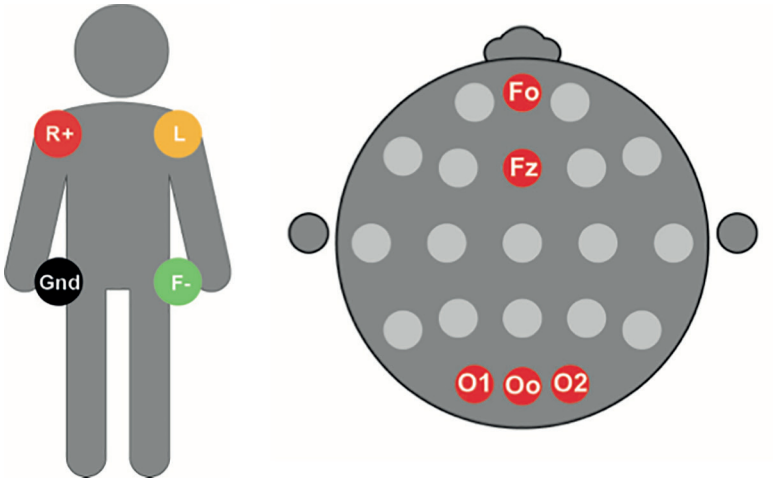

Figure 1. Schematic representation of electrode positions. Left panel depicts electrode positions on the rump. R, Right Arm; L, Left Arm; F, Foot; Gnd, Ground. Right panel represents electrode positions on the head in the 10/20 system. Positions F0, Fz, O1, Oo and O2 were used (marked in red).

For the immersed condition, a saline solution at 37 degrees Celsius was used to simulate similar conductive conditions as the amniotic fluid (electrical conductivity of $1.6*10^{-4}$ $Ohm^{-1}cm^{-1}$).[6] The subject was lying in a bathtub in supine position and breathing through a snorkel. The ECG was measured in two consecutive sessions. First in dry, then in immersed condition. During both sessions, the same protocol of head orientations was followed: head neutral, anteflexion, right rotation, left rotation and deflexion. Figure 2 depicts the body orientations. Each head orientation was

maintained for 20 seconds, with the subject holding its breath after exhalation. The experiment was conducted twice to evaluate reproducibility.

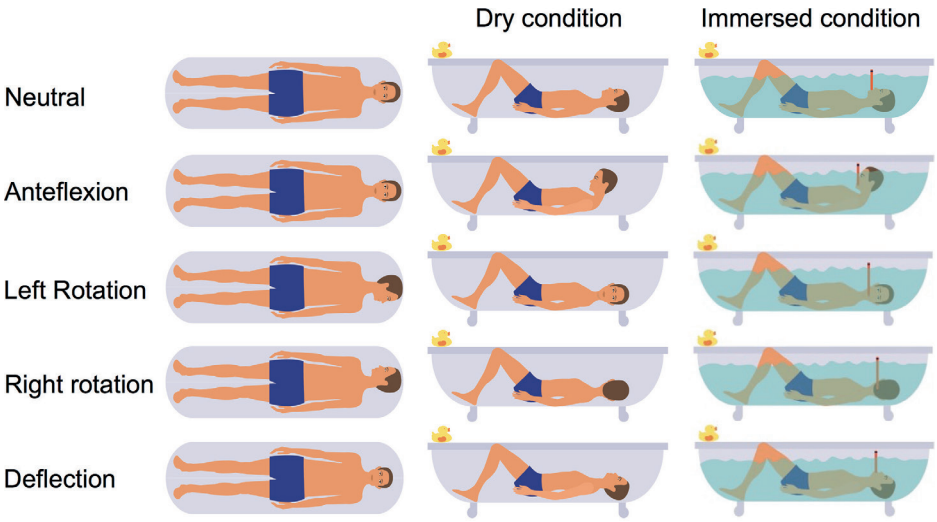

Figure 2. Body orientations. The panel shows five body orientations from top view, side view in dry condition, and side view in immersed condition, consecutively.

Data-processing

The electrodes were connected to a commercial amplifier for electrophysiological measurements (Porti, TMsi, the Netherlands). All data were stored and processed offline. Data from the first and final 2 seconds during a head orientation were discarded to exclude potentially poor quality signals during the transition from one head orientation to the next. The signals were pre-processed by applying a band-pass filter between 2-150 Hz to minimize the effects of low frequency baseline drift and high frequency noise. A 50-Hz notch filter was used to suppress the powerline interference.

After pre-processing, one average ECG complex was calculated for each electrode position in each head orientation in both dry and immersed condition as a unipolar and a bipolar lead. At first, the R-peaks were detected with a wavelet-based R-peak detection algorithm.[7] Subsequently, individual ECG complexes were aligned on their R-peak locations and an initial average ECG complex was calculated from these aligned ECG complexes. Then, each individual ECG complex was compared to this average ECG complex. Individual ECG complexes with a correlation of less than 0.9 with the average ECG complex were excluded for further analysis. The average

ECG complex was re-calculated using only the included ECG complexes. Finally, based on the average ECG complex, the ST-segment was detected as the segment from S-peak to end of the ECG complex. In the ST-segment, a moving-average-filter of length 10 ms was used to further reduce the influence of high frequency noise.

The ratio between T-amplitude and QRS-amplitude (T/QRS ratio) was calculated from the filtered average ECG complex. To that end, the ECG baseline was determined based on the isoelectric period between P-wave and QRS-complex. Next, T-amplitude was calculated as the difference between T-peak and ECG baseline. Subsequently, QRS-amplitude was calculated as the maximum difference between R-peak and either Q- or S-peak. A T/QRS ratio was determined for every unipolar lead in all 5 head orientations in both dry and immersed conditions. These T/QRS values were used as outcome measure to compare the amplitudes of the ECG waveform between all conditions.

Results

Table 1 and Table 2 present all T/QRS ratios in the unipolar leads in dry and immersed condition, for all electrode positions and head orientations for experiment 1 and 2, respectively.

During the dry condition we observed little to no difference in T/QRS ratio between different electrode positions (maximal difference between 0.00 and 0.01) in the unipolar leads. We observed minor differences in T/QRS ratio between head orientations (maximal difference between 0.02–0.03). During the immersed condition, the maximal T/QRS difference varied between 0.02–0.05 for electrode positions, and between 0.03–0.06 for head orientations, respectively. Figure 3 depicts examples of ECG complexes and T/QRS values in dry and immersed condition respectively (left panel versus right panel).

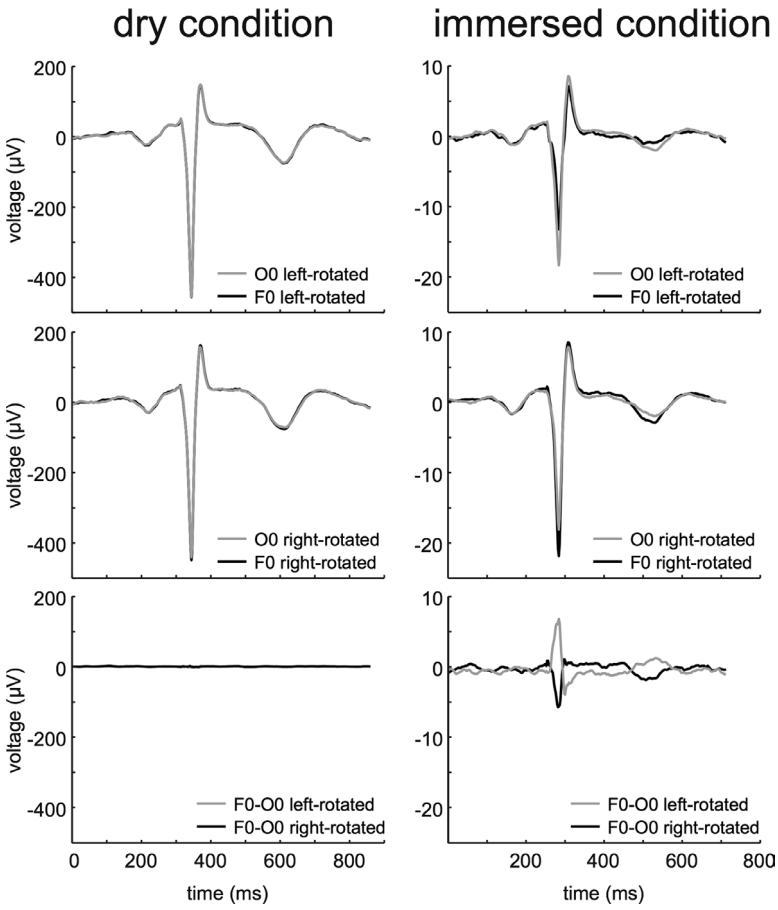

Figure 3. Examples of ECG complexes in dry and immersed condition. Unipolar (O0 and F0) and bipolar (F0-O0) scalp electrode signals with left- or right-rotated head during dry or immersed conditions.

Table 1. T/QRS ratios in dry and immersed conditions (Experiment #1).

Exp #1 Dry	Head neutral	Anteflexion	Rightward rotation	Leftward rotation	Deflexion	Maximal Δ
F0	0.19	0.17	0.18	0.18	0.17	0.02
Fz	0.19	0.17	0.18	0.18	0.17	0.02
O0	0.19	0.17	0.17	0.18	0.17	0.02
O1	0.19	0.17	0.18	0.18	0.17	0.02
O2	0.19	0.17	0.17	0.18	0.17	0.02
Maximal Δ	0.00	0.00	0.01	0.00	0.00	
Exp #1 Immersed	**Head neutral**	**Anteflexion**	**Rightward rotation**	**Leftward rotation**	**Deflexion**	**Maximal Δ**
F0	0.14	0.12	0.16	0.13	0.12	0.04
Fz	0.16	0.17	0.16	0.16	0.12	0.05
O0	0.15	0.16	0.14	0.14	0.13	0.03
O1	0.13	0.16	0.13	0.14	0.11	0.05
O2	0.14	0.15	0.12	0.13	0.13	0.03
Maximal Δ	0.03	0.05	0.04	0.03	0.02	

T/QRS values are presented per unipolar scalp electrode position and head orientation. The maximal difference in T/QRS ratio between the electrode positions per head orientation, and between head orientation per electrode position is presented in the final columns and rows, respectively. Abbreviations: Exp #, experiment number.

Table 2. T/QRS ratios in dry and immersed conditions (Experiment #2).

Exp #2 Dry	Head neutral	Anteflexion	Rightward rotation	Leftward rotation	Deflexion	Maximal Δ
F0	0.18	0.17	0.19	0.17	0.17	0.02
Fz	0.17	0.17	0.19	0.17	0.17	0.02
O0	0.17	0.16	0.19	0.17	0.17	0.03
O1	0.17	0.16	0.19	0.17	0.17	0.03
O2	0.17	0.16	0.19	0.17	0.17	0.03
Maximal Δ	0.01	0.01	0.00	0.00	0.00	
Exp #2 Immersed	**Head neutral**	**Anteflexion**	**Rightward rotation**	**Leftward rotation**	**Deflexion**	**Maximal Δ**
F0	0.13	0.14	0.12	0.12	0.11	0.03
Fz	0.13	0.12	0.13	0.11	0.07	0.06
O0	0.10	0.10	0.09	0.12	0.08	0.04
O1	0.09	0.09	0.08	0.11	0.06	0.05
O2	0.10	0.10	0.09	0.13	0.08	0.05
Maximal Δ	0.04	0.05	0.05	0.02	0.05	

T/QRS values are presented per unipolar scalp electrode position and head orientation. The maximal difference in T/QRS ratio between the electrode positions per head orientation, and between head orientation per electrode position is presented in the final columns and rows, respectively.
Abbreviations: Exp #, experiment number.

The first and second row show contrasting electrode positions of unipolar leads O0 and F0. In dry condition, ECG waveform was similar in both leads, whether the head was left- or right-rotated. In contrast, in immersed condition the top row (head left-rotated) shows lower R and T peak amplitudes measured at the frontal lead (F0) compared to the occipital lead (O0). The middle row (head right-rotated) shows higher R and T peak amplitudes at the frontal compared to the occipital lead.

The bottom row of Figure 3 shows bipolar leads in both dry and immersed conditions. The left panel shows the bipolar leads in dry condition in left rotation and right rotation. No recognizable ECG signal could be estimated, as the electric potential differences between the electrodes were too small and noise-generated. In immersed condition however (right panel, third example), bipolar leads showed a recognizable ECG pattern, which differs in contrasting head orientations.

Discussion

In this experimental study we examined the influence of electrode position and head orientation on the waveform of a single lead unipolar scalp ECG when recorded in a conductive medium. In dry condition ECG waveform was similar in all positions and orientations. In contrast, in immersed condition we observed ECG waveform differences between differently positioned electrodes at the scalp and between different head orientations.

We found that ECG waveform is independent of electrode position on the head in dry condition. The frontal and the occiput electrodes reflect the maximal possible difference between electrodes (F0-O0). Even these electrodes showed a similar ECG waveform in our experiment. In dry condition, cardiac currents are solely conducted through the body from the heart to the electrode at the scalp. As such, all electrode positions on the head reflect the same lead as the extension of the neck. In case head orientation towards the body changes, the path of the cardiac currents to the electrodes on the scalp remains equal. Hence, little to no influence was seen on the ECG waveform for different electrode positions (maximum variation was 0.01). We observed some minor variation between T/QRS value for different head orientations (maximum variation was 0.03). As different head orientations can only be measured consecutively and not simultaneously, factors changing over time, like lung air volume and distance to bath may influence ECG waveform. Additionally,

flexing of the neck might yield some stress on the thorax and cause minor movement of the heart.

In immersed condition, we observed different ECG waveforms for the various electrode positions and head orientations. We showed that head rotations cause a change in absolute and relative T/QRS values. We also showed that the T/QRS baseline value differs between electrode locations, which may influence the amount of ST events in ST analysis. Vullings et al. showed that fetuses with a higher initial T/QRS baseline value have more ST events, irrespective of fetal condition.[8] The maximal difference in T/QRS between electrode positions was 0.05 and the maximal difference in T/QRS for different head orientations was 0.06. These differences in T/QRS values during immersed conditions can be explained because the electrical currents generated by the heart propagate to the scalp electrode both intracorporally and extracorporally (i.e., through the saline medium). The path of extracorporal conduction depends on the distance, position and presence of conductive media between the electrode and the heart, which varies for different electrode positions and head orientations. These differences in conduction path result in changes in the ECG amplitudes for each electrode and head orientation.

Besides larger changes in T/QRS values for immersed condition, we also observed lower absolute ECG amplitudes compared to the dry condition, as is seen from the amplitudes of the ECGs in Figure 3. In our experiment, we measured the ECG as a unipolar signal, where the difference between the scalp electrodes and the WCT is amplified. This difference is reduced during immersed conditions, due to the increased similarity of the scalp ECG and the WCT. It should be noted, however, that amplitudes of QRS-complex and T-wave were similarly suppressed. Therefore, we expect the effect of similarity between scalp electrode signal and WCT to be of little influence on T/QRS values.

Although we observed a more significant influence of electrode position and head orientation on the ECG waveform during immersed conditions for both experiment 1 and 2, results regarding changes in size of the T/QRS ratios were inconsistent. For example, in experiment 1, electrode O2 showed a difference of 0.01 in T/QRS between head oriented towards the right versus the left shoulder. On the contrary, experiment 2 showed a difference of 0.04 when the same head orientations were compared. These inconsistencies may be related to different conditions under which the experiments were conducted, such as lung air volume, electrode fixation, precise electrode positioning, magnitude of head movement, distance between electrode and bath tub, and water temperature. Although we attempted to minimize these

effects, e.g. by only recording the ECG after complete exhalation and controlling water temperature, these conditions cannot be fully controlled. In future work, this experiment should be repeated multiple times in different individuals to enable more quantitative analysis of changes in ECG waveform.

Lindecrantz et al. compared fetal ECG morphology measured by bipolar and unipolar leads.[9] They found that, in case of bipolar measurements, the scalp ECG can invert due to the rotation of the fetal head during passage through the birth canal. We found comparable results in bipolar lead measurements in immersed condition. Altered electrode position and head orientation influence ECG waveform, as evidenced in Figure 3 where we show that under immersed conditions the ECG-waveform differs between contrasting head position (head rotated towards left or right shoulder, respectively). Because Lindecrantz et al. did not find any effect on ECG waveform due to head rotation in unipolar lead measurements, they suggested that this unipolar technique would be appropriate for fetal monitoring. We however now show that in immersed condition even unipolar lead signals are influenced by electrode position and head orientation.

This study has some limitations, which imply that extrapolating results to the fetal situation should be done with caution. The set up of this experiment is a simplified environment in comparison to the fetal situation and it does not include the effect of electrical currents from maternal tissues. We hypothesized that the fetal situation is comparable to the immersed condition. Besides, the sample size is limited to two experiments. To examine the effect of surrounding tissues on the waveform of the fetal scalp ECG in clinical practice would require comprehensive denotation or correction of the scalp electrode position and fetal head orientation during all stages of labor. This seems practically unfeasible. However, clinicians should be aware that fetal condition is not the only factor influencing the waveform of the fetal scalp ECG.

Conclusions

In conclusion, in this experimental study we demonstrated that ECG waveforms recorded from unipolar as well as bipolar scalp leads are influenced by electrode position and head orientation when the subject is submerged in a conductive medium. This implies that intrapartum fetal monitoring based on ECG waveform obtained using scalp electrodes might be suboptimal, as there is no correction for fetal head neither orientation nor electrode position.

Supplementary materials

The supplementary materials contain the following tables and can be accessed via the corresponding links:

- **Table S1.** Digital average ECG complexes of experiment #1 for the 5 unipolar scalp electrodes in 6 positions under dry circumstances.
  https://doi.org/10.1371/journal.pone.0223282.s001

- **Table S2.** Digital average ECG complexes of experiment #1 for the 5 unipolar scalp electrodes in 6 positions while immersed.
  https://doi.org/10.1371/journal.pone.0223282.s002

- **Table S3.** Digital average ECG complexes of experiment #2 for the 5 unipolar scalp electrodes in 6 positions under dry circumstances.
  https://doi.org/10.1371/journal.pone.0223282.s003

- **Table S4.** Digital average ECG complexes of experiment #2 for the 5 unipolar scalp electrodes in 6 positions while immersed.
  https://doi.org/10.1371/journal.pone.0223282.s004

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CHAPTER 5

Relative versus absolute rises in T/QRS ratio by ST analysis of fetal electrocardiograms in labour: A case-control pilot study

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Abstract

Introduction

The additional value of ST analysis during labour is uncertain. In ST analysis, a T/QRS baseline value is calculated from the fetal electrocardiogram and successive T/QRS ratios are compared to this baseline. However, variation in the orientation of the electrical heart axis between fetuses may yield different T/QRS baseline values. In case of a higher T/QRS baseline value more ST events are encountered, although not always related to perinatal outcome. We hypothesised that we can partly correct for this effect by analysing T/QRS rises as a percentage from baseline (relative ST analysis). This study aimed to explore whether relative ST analysis has better diagnostic value for cord acidaemia compared to conventional ST analysis, where predefined fixed T/QRS ratios are used.

Methods and materials

A case-control study was performed in 20 term human fetuses during labour; 10 cases (umbilical cord artery pH <7.05 at birth, defining acidaemia) and 10 controls (pH >7.20) were included. The fetal electrocardiogram was recorded using a STAN monitor. We electronically extracted all T/QRS values, baseline and episodic ST events from the STAN monitor and calculated the relative T/QRS changes. The cut-off for relative ST events was determined in a receiver operator characteristic (ROC) curve at optimal specificity for cord acidaemia. Parameters of interest were area under the curve (AUC) of the ROC curve for relative ST events and test performance of both conventional and relative ST analysis.

Results

Relative ST analysis showed an AUC of 0.99. The optimal cut-off value for relative T/QRS rise was determined at 0.70. Relative vs conventional (absolute) ST analysis showed a specificity of 100% vs 40% (p = 0.031); sensitivity 90% vs 90%; positive likelihood ratio infinity vs 1.5; negative likelihood ratio 0.10 vs 0.25, respectively.

Conclusion

Relative ST analysis seems to be a promising method to detect impending fetal acidaemia during labour. Further studies are required to determine the diagnostic accuracy.

Introduction

Fetal surveillance during labour, although performed continuously in labour wards around the world, is still a topic of debate. Due to poor specificity of cardiotocography (CTG), unnecessary caesarean deliveries are performed without improvement in long-term neonatal outcome.[1] ST analysis of the fetal electrocardiogram (ECG) (STAN, Neoventa Medical AB, Mölndal, Sweden) was introduced in the 1990s as a promising technique to accurately detect impending metabolic acidosis and improve perinatal outcome.[2] Metabolic acidosis can be objectively measured as the umbilical cord arterial pH and base deficit. Acidaemia in the umbilical cord is a marker of fetal distress during labour and is, most frequently, caused by hypoxia due to contractions. Two large randomised trials (RCTs), both comparing CTG monitoring alone to CTG monitoring plus ST analysis, showed promising results with a decrease in metabolic acidosis[3] and operative deliveries.[2,3] Subsequent RCTs did not confirm these results[4-7] and meta-analyses report both significant and non-significant decreases in metabolic acidosis.[8-11]

The physiological rationale of ST analysis is based on the finding of Rosén et al.[12-14] that hypoxia in fetal lambs leads to an adrenalin surge, resulting in local glycogenolysis and potassium release in the fetal myocardium. This local increase in potassium ions leads to an increase in T wave amplitude in the fetal ECG.[12,14,15] In ST analysis this T wave amplitude is quantified as the ratio between the T wave amplitude and the QRS amplitude, the so-called T/QRS ratio. At the start of the fetal ECG registration, a T/QRS baseline is determined in a 2-step procedure. First, for every T/QRS ratio a median is calculated over the last 20 preceding T/QRS ratios. Then, the T/QRS baseline is defined as the lowest value of these median T/QRS ratios within a three hour window preceding the current T/QRS ratio. At the same time, for every T/QRS ratio another median is calculated over the last 10 preceding T/QRS ratios, from here on defined as T/QRS-med10. In case there is a rise in T/QRS ratio, defined as a difference between T/QRS ratios and the baseline, that exceeds a predefined threshold, an alarm is automatically triggered and reported by the STAN monitor. ST analysis discriminates three types of events (alarms): episodic, baseline, and biphasic events. In case T/QRS-med10 exceeds the baseline by 0.05 — analogous to a rise of T/QRS ratios above the baseline for at least 10 minutes — a baseline ST event is reported.[15] When the current T/QRS ratio exceeds the T/QRS-med10 by 0.10 — analogous to a rise of T/QRS that lasts shorter than 10 minutes — an episodic ST event is reported. Both episodic and baseline events represent an absolute increment of the T/QRS ratio compared to the T/QRS baseline. Biphasic ST events are defined as ST intervals with a downward slope.[15] The relevance of a ST event depends on the

visual assessment of the CTG. In case the CTG is classified as normal, all ST events given by the STAN monitor can be ignored.[16-18] In that case, the ST event is classified as a non-significant event. In clinical practice, such non-significant events are frequently encountered.[19] In case the CTG is classified as intermediary or abnormal, depending on the classification of the CTG trace, ST events might be considered to be significant and a clinical intervention should be prompted.[18] The dependence on subjective CTG interpretation, which is known to have a large inter- and intra-observer variability[1,20], is the Achilles' heel of CTG plus ST analysis in clinical practice.

Previously, we described a physiological explanation for false positive ST events and hypothesised that relative ST analysis (T/QRS rises as a percentage from baseline) could reduce these false events. We demonstrated that the orientation of the fetal electrical heart axis varies considerably between fetuses.[21] The relation between the orientation of the electrical heart axis and the orientation of the scalp electrode yields different T/QRS baseline values, due to differences in ECG morphology. We found that fetuses with a higher T/QRS baseline are more prone to ST events, independent of the fetal condition.[22] In contrast, we found that fetuses with a lower T/QRS baseline are less prone to exceed the threshold for a ST event. In other words, it is expected that a high initial T/QRS baseline increases the incidence of false positive ST events and that a low initial T/QRS baseline increases the incidence of false negative ST events. Besides, Becker et al.[23] described that higher T/QRS baseline values are not related to poor neonatal outcome or hypoxia.

Both the T/QRS baseline value and the rise in T wave amplitude are affected by the orientation of the electrical heart axis, although to different extents. The amplitude of the QRS complex and amplitude of the T wave in the ECG reflect the amplitude of the electrical activity of the heart in the direction of the scalp lead. The ECG amplitude depends on both the amount of electrical activity and the orientation of this activity, i.e. the geometrical angle between the direction of the electrical activity and the direction of the scalp lead. Because the electrical activity of the QRS complex and the T wave have different orientations with regard to the scalp lead, variations in the orientation of the electrical heart axis affect the QRS complex and the T wave to different extents, hence affecting the T/QRS ratio.

As mentioned above, we hypothesised that analysing relative, rather than the conventional, 'absolute' T/QRS rises from baseline, could improve the diagnostic value of ST analysis. In case of relative ST analysis (RSTAN) (T/QRS rises as a percentage from baseline), there is a correction for the 'ease' of increment of the T wave amplitude. In conventional absolute ST analysis (ASTAN), an absolute rise in T/QRS value

will lead to an event when above a certain predefined fixed increase, irrespective of the height of the T/QRS baseline. This study aimed to explore the prospect whether RSTAN could have a diagnostic value in detecting impending cord acidaemia. In addition, we aimed to compare sensitivity, specificity, positive and negative likelihood ratios of both RSTAN and ASTAN. This is the first study that describes RSTAN. In order to directly compare both methods, we only focused on objective information. Therefore, we omitted subjective CTG interpretations.

Materials and methods

Patient inclusion

We performed a case-control study, using the complete dataset previously collected by van Laar et al.[24] The ethics committee of Máxima Medical Centre decided that there was no need to acquire written informed consent from the included patients given the retrospective nature of this study. The criteria for inclusion were equal to those in the original dataset.[24] We included fetuses of at least 36 weeks of gestation with intrapartum fetal ECG recordings, whose arterial and venous umbilical cord blood gases were determined directly after birth. The included mothers were healthy, had an uncomplicated pregnancy and did not use any medication except oxytocin or epidural analgesia during labour. We only included fetuses with a normal 20 week anomaly scan including echocardiography. Only good quality fetal ECG recordings were included, defined as absence of ectopic beats and no missing data in the last 10 minutes before birth. We excluded fetuses with fetal growth restriction (defined as birth weight below the 10th percentile), because these fetuses might have myocardial hypertrophy with, hypothetically, a deviated heart axis.[25-27] For all 20 fetuses, good quality ECG data were available until nine minutes before birth. In nine fetuses (four cases, five controls), fetal ECG data could be obtained until the last minute before birth. The median duration of the recordings was 277 minutes, the duration ranged from 42 to 524 minutes.

Cases had an umbilical artery cord pH <7.05 and controls had an umbilical artery cord pH >7.20. We chose the cut off at pH >7.20 for the controls as it represents the upper range of normality and represents the group of uncompromised fetuses. Cases were consecutively selected between January 2006 and December 2007 in the Máxima Medical Centre, Veldhoven, the Netherlands. As a result of the strict inclusion and exclusion criteria, only five fetuses with acidaemia could be included. Therefore, five additional fetuses with acidaemia were consecutively selected from the University Medical Centre Utrecht, the Netherlands, between January 2001 and

July 2002. Both hospitals are tertiary-care teaching hospitals. The ten controls were consecutively selected between January 2007 and August 2007 in the Máxima Medical Centre, Veldhoven, the Netherlands.

Signal processing

Fetal ECG recordings were obtained during labour with a single helix scalp electrode (Goldtrace), a maternal skin electrode, and STAN S21 or S31 monitors (Neoventa Medical AB, Mölndal, Sweden). The STAN monitor detected an ECG complex for every heartbeat. After 30 good quality ECG complexes, an average ECG complex was automatically calculated. This average ECG complex was used to determine the amplitudes of the T wave and QRS complex which, in turn, were used to calculate a single T/QRS ratio after every 30 heart beats (Figure 1). We extracted all these T/QRS ratios from all registrations.

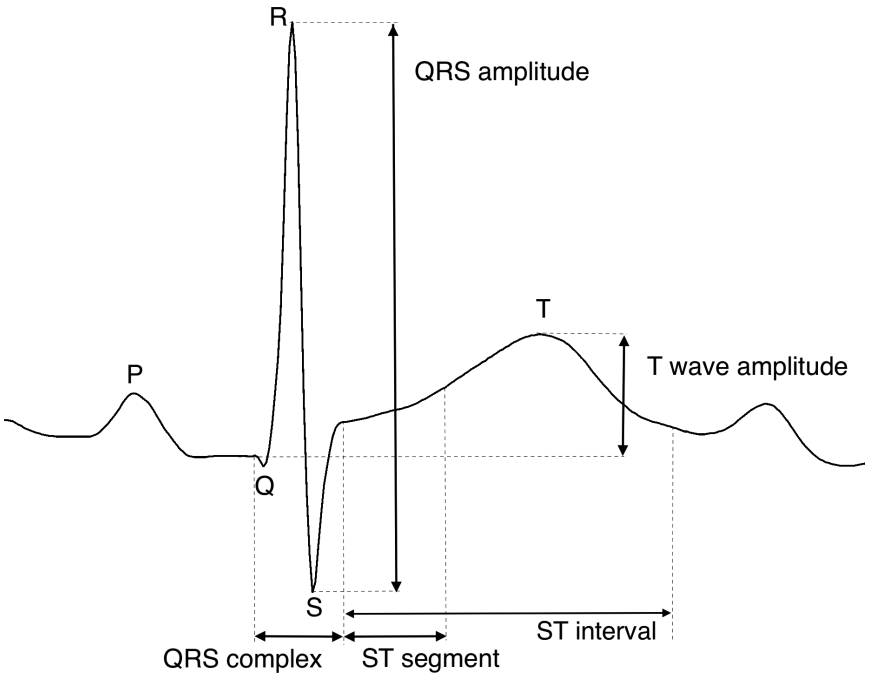

Figure 1. Schematic ECG parameters. The T/QRS ratio is the quotient of T amplitude and QRS amplitude.

The STAN monitor automatically reports episodic, baseline and biphasic events in an 'event log'. We used this 'event log' in the STAN viewer software (Neoventa) to determine whether baseline or episodic ST events occurred. Biphasic events were not evaluated in this study, since only baseline dependent ST events are known to be related to the orientation of the electrical heart axis.[22] In addition, the value of biphasic events is under debate, as recent studies showed they do not discriminate in the prediction of fetal distress or adverse outcome.[19,28,29]

For RSTAN, instead of assessing the difference between T/QRS ratios and the baseline, we calculated the quotient. We defined the baseline equally to the STAN method as described in the Introduction. In case the 20 consecutive preceding T/QRS ratios did not fall within a 20-minute window from the current T/QRS ratio, we classified the signal as low quality and did not update the baseline (the baseline remained unchanged; this method is similar as in the STAN monitor). All calculations were performed electronically in Matlab (The Mathworks, Natick, MA). To determine the optimal threshold for RSTAN, the largest T/QRS rise from baseline per patient was plotted in a receiver operating characteristic curve (ROC curve) in SPSS 22 for Mac (IBM corp. Armonk, NY, USA). The ROC curve was calculated under non-parametric assumption. The cut-off points for which sensitivity and specificity were calculated were chosen by SPSS. The smallest cut-off value was the minimum observed relative T/QRS rise minus 1, and the largest cut-off value is the maximum observed relative T/QRS rise plus 1. The other cut-off values were the averages of two consecutive ordered observed relative T/QRS rises. The optimal threshold to predict umbilical cord arterial acidaemia was determined from the ROC curve (the point closest to (0,1)).

As mentioned previously, we wanted to assess the test performance of ASTAN and RSTAN in a cohort of 10 cases and 10 controls. Ideally, alarms should appear in the pH <7.05 group (cases). On the other hand, we would expect no alarms in the pH >7.20 group (controls). We considered a registration to have at least one relative ST event, in case the largest relative T/QRS rise in a registration exceeded the previously defined threshold for RSTAN. To assess whether there was an absolute ST event, we checked whether the event log of the STAN monitor reported any baseline or episodic ST event. We omitted biphasic ST events. In addition, we reported whether there where any absolute or relative ST events in the last 42 minutes of the registration, which was the duration of the shortest registration. To omit subjective interpretation of the CTG, no CTG classification was performed. Therefore, absolute ST events were not classified as significant or non-significant. Instead, we classified the events as true or false, based on whether the patient was a case or a control.

Table 1. Patient characteristics.

Characteristic	Cases (n = 10)		Controls (n = 10)	
Nulliparous–n (%)	8 (80)		4 (40)	
Gestational age–days	283 ±8	283 [269–295]	278 ±11	279 [259–294]
Epidural analgesia–n (%)	3 (30)		3 (30)	
Oxytocin–n (%)	7 (70)		4 (40)	
FSBS–frequency	1.4	2 [0–3]	0	0
Birth weight–gram	3414 ±423	3375 [2910–4110]	3643 ±562	3690 [2770–4500]
Arterial pH	6.98 ±0.07	7 [6.82–7.04]	7.26 ±0.03	7.26 [7.20–7.29]
Arterial Base Excess–mmol/l	-17.3 ±4.0	-17 [11–26]	-5.2 ±2.0	-5.5 [2.0–9.0]
Venous pH	7.08 ±0.10	7.09 [6.87–7.19]	7.33 ±0.04	7.34 [7.25–7.39]
Hospital admission–n (%)	4 (40)		0 (0)	
Ventouse delivery* –n (%)	4 (40)		0 (0)	

Abbreviations: FSBS = fetal scalp blood sampling. Continuous variables are presented as both mean ± standard deviation and median [total range minimum-maximum].

*None of the included patients had a cesarean or forceps delivery.

Statistical analysis

Patient characteristics were listed in Table 1. Categorical variables were presented as frequency and percentage. Continuous variables were presented both as mean and standard deviation, and median and total range. We reported the area under the receiver operating characteristic (AUC) for RSTAN and the p value (compared to the null hypothesis of an AUC of 0.5). We used a ROC curve to determine a threshold for RSTAN at the point closest to (0,1) and at optimal specificity. This threshold was subsequently used to compute positive and negative likelihood ratios of RSTAN. RSTAN and ASTAN were compared with respect to sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) to detect impending umbilical cord acidaemia (pH <7.05). We used a McNemar test to compare RSTAN to umbilical cord arterial acidaemia, ASTAN to umbilical cord arterial acidaemia, specificity between RSTAN and ASTAN and sensitivity between ASTAN and RSTAN. A p-value <0.05 was considered to be statistically significant. In addition, we tested agreement between RSTAN and ASTAN with Cohen's unweighted Kappa and the composite proportions of agreement with VassarStats online software (Lowry, Avon, USA Available from: http://vassarstats.net).

Results

Patient characteristics

Table 1 shows the patient characteristics. None of the included patients had a cesarean section or forceps delivery. Four cases had a ventouse delivery; no operative deliveries were performed in the control group.

Relative versus absolute ST analysis

Figure 2 shows the ROC curve for RSTAN. The area under the ROC curve for relative T/QRS ratio changes in this population was 0.99 (p <0.001). Two optimal cut-off values were determined, at a relative T/QRS ratio rise of 0.64 (specificity 90%, sensitivity 100%) and 0.70 (specificity 100%, sensitivity 90%), respectively. Both cut-off values were equally close to (0,1). We chose to use 0.70 as cut-off for the subsequent analyses (i.e. a 70% rise of the T/QRS ratio from baseline), as it had better specificity and poor specificity is the main problem of the available monitoring techniques.

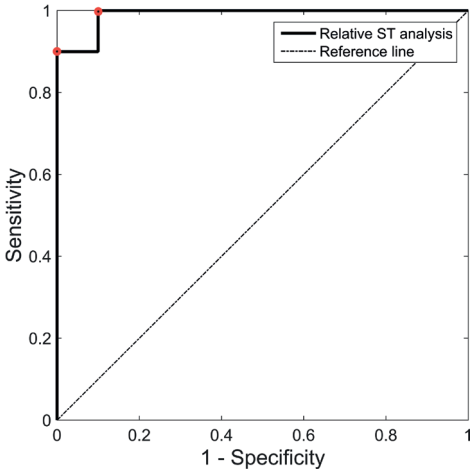

Figure 2. Receiver operating characteristic (ROC) curve of relative ST analysis. The ROC curve was calculated under non-parametric assumption. The two highlighted points (red dot) represent the cut-offs closest to (0,1) at a relative T/QRS ratio rise of 0.64 (sensitivity 100%, specificity 90%) and 0.70 respectively (sensitivity 90%, specificity 100%).

Figure 3 shows an example of an ECG at the beginning of the registration and during an event in a control (A) and a case (B) respectively. It illustrates that for a patient with pH >7.20 a change in T/QRS ratio can occur that is classified as an absolute ST event without being a relative ST event (control). Vice versa, for a patient with pH <7.05, a change in T/QRS ratio can occur that is not classified as a absolute ST event, but that is classified as a relative ST event (case).

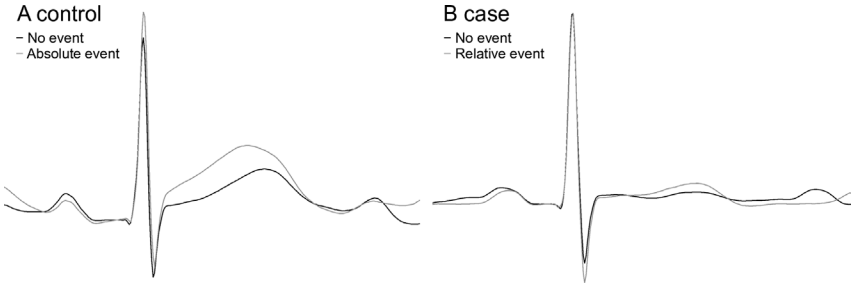

Figure 3. ECG examples. Panel A shows an example of an ECG in a control (pH >7.20) at the beginning of the registration (black) and during an absolute (episodic) ST event (grey). The absolute rise in T/QRS ratio here exceeds 0.10, whereas the relative T/QRS rise does not exceed 0.70 (no event). Panel B shows an ECG in a case (pH <7.05) at the beginning of the registration (black) and during a relative ST event (relative rise from baseline is 1.25) (grey). The absolute T/QRS rise is here below 0.05 (no absolute ST event).

We compared the test performance of ASTAN and RSTAN in our study population (Tables 2 and 3). Sensitivity was equal for both methods, while specificity, LR+, and LR- seemed to be better for RSTAN.

Table 2. Crosstable of relative and absolute ST analysis.

		Case: pH <7.05 (n = 10)	**Control: pH >7.20 (n = 10)**
Relative ST analysis	Event	9	0
	No event	1	10
Absolute ST analysis	Episodic or baseline event	9	6
	No event	1	4

Relative ST analysis was defined as at least one relative T/QRS rise from baseline over 70%. Absolute ST analysis was defined as at least one reported baseline or episodic event in the event log. None of the cases had any episodic event. 4 controls had solely baseline events, 1 control had at solely episodic events, and 1 control had both baseline and episodic events.

Table 3. Test performance of absolute and relative ST analysis to detect impending cord acidaemia (pH <7.05).

	Absolute ST analysis	**Relative ST analysis**
True positive — n/total	9/10	9/10
True negative — n/total	4/10	10/10
Sensitivity	0.9	0.9
Specificity	0.4	1.0
Positive likelihood ratio	1.5	∞
Negative likelihood ratio	0.25	0.1

Absolute ST analysis was defined as at least one reported baseline or episodic event in the event log. Relative ST analysis was defined as at least one relative T/QRS rise over 70% from baseline. Test performance was depicted as sensitivity (true positives/(true positives + false negatives)), specificity (true negatives/(true negatives + false positives)) positive likelihood ratio (sensitivity/(1 – specificity)) and negative likelihood ratio ((1 – sensitivity)/specificity). Positive outcome was defined as cord artery acidaemia (pH <7.05).

In addition, we compared the presence of absolute and relative ST events in the last 42 minutes of each registration (same registration length). ASTAN and RSTAN

showed a sensitivity of respectively 70% and 60% and specificity of respectively 60% and 100%.

When using a cut-off value of 0.70 as threshold for RSTAN, RSTAN and ASTAN had comparable sensitivity (McNemar p = 1.000), but differed significantly regarding specificity (McNemar p = 0.031) to discriminate acidaemic and non-acidaemic fetuses. Overall, RSTAN agreed well with cord acidaemia (McNemar p = 1.000), while ASTAN tended to agree less well (McNemar p = 0.125). RSTAN and ASTAN showed a weak agreement (Cohen's unweighted kappa 0.42). The composite proportion of agreement between RSTAN and ASTAN was moderate (0.72).

Discussion

This study explored the possibility whether RSTAN in comparison with ASTAN could have a better diagnostic accuracy in detecting umbilical cord arterial acidaemia, while restricting the number of false positive events. We found that RSTAN may improve the identification of fetuses with impending acidaemia at birth. To explore whether RSTAN could solve the frequently occurring problem of non-significant ST events with ASTAN[19], we compared the sensitivity and specificity of both methods. In this pilot study, in which 50% of the included patients had cord blood acidaemia, RSTAN indicated to have a better specificity, and a trend towards better positive and negative likelihood ratios. Sensitivity was equal. The agreement between ASTAN and RSTAN was weak to moderate, indicating that RSTAN might be better in identifying impending cord acidaemia during labour.

In ASTAN, non-significant ST events are frequently encountered.[20] This could lead to alarm fatigue of the staff, which might have deleterious consequences for both the mother and child. This study indicated that ST monitoring with correction for orientation of the electrical heart axis may be capable of identifying fetuses with acidaemia without showing many false positive events. However, as CTG interpretation was not included in the study, it is unknown whether ASTAN events would have been classified as truly significant or non-significant. We suggest that as a topic for further studies.

In case comparing the last 42 minutes of each registration, sensitivity of RSTAN was 60%, while it was 90% in the total registration. This difference can be explained by the fact that a shorter registration misses earlier RSTAN events.

Lee et al. described that the electrical heart axis may change during tachycardia and decelerations.[30] We are aware that this could introduce a bias in both ASTAN and RSTAN methods. However, we expect this error to be smaller in RSTAN, as this method corrects for variations of the electrical heart axis.

Although the results from this first study describing RSTAN are promising, there are some important limitations. We did not evaluate the full spectrum of patients in a clinical setting, since only cases with proven acidaemia and controls with normal umbilical cord pH values at birth were included. A large middle group with umbilical cord pH between 7.05 and 7.20 was not represented, Furthermore, the study sample size was small; only 10 cases and 10 controls, which makes the risk of both type I and type II errors high.

Taken the limitations of our study into account, validity of RSTAN should be evaluated in a larger patient group, including the full spectrum of perinatal outcomes. This would allow to determine a more reliable and representative threshold value for RSTAN. Subsequently, such a threshold should then be validated in a different group of patients. We then expect that the test characteristics of RSTAN will be less optimistic than those found in the current work. Unfortunately, there is a lack of large datasets with high quality fetal ECG data stored electronically, accompanied by complete and relevant clinical information. This delays further progress in this field of research.

Conclusion

This study indicates that relative T/QRS analysis is a promising technique to detect impending fetal acidaemia during labour. In comparison to conventional absolute ST analysis, relative ST analysis might have better specificity with a comparable sensitivity. Relative ST analysis seems to be a promising method for monitoring of fetal wellbeing during labour and needs to be studied in a larger population.

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CHAPTER 6

Adapted ST analysis during labor: relative versus absolute ST events, a case-control study

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Abstract

Background

The value of ST analysis of the fetal electrocardiogram during labor to lower asphyxia and cesarean section rates is uncertain. Physiological variation of the electrical heart axis between fetuses may explain false alarms in conventional ST analysis (absolute ST analysis). ST events (alarms) based on relative T/QRS rises (relative ST analysis) correct for this variation and may improve diagnostic accuracy of ST analysis.

Aims

To compare the diagnostic accuracy of absolute and relative ST analysis with regard to fetal acidemia.

Study design

Retrospective case-control study.

Subjects

20 healthy women with an uncomplicated pregnancy monitored with ST analysis during labor: 10 cases (umbilical cord artery pH <7.05) and 10 controls (pH >7.20).

Outcome measures

Sensitivity, specificity, positive and negative likelihood ratio.

Results

In 16 of the 20 patients a total of 54 absolute ST events were reported. Two reviewers classified the cardiotocograms; in cases 29% of the absolute ST events were significant, in the controls it was 19%. Relative ST analysis versus absolute ST analysis showed a sensitivity of 90% (55–100%) vs. 70% (35–93%), a specificity of 100% (69–100%) vs. 70% (35–93%), a positive likelihood ratio of infinity vs. 2.3 (0.8–6.5), a negative likelihood ratio of 0.1 (0.0–0.6) vs. 0.4 (0.2–1.2), and diagnostic odds ratio of infinity vs. 5.4 (0.8–36.9). McNemar showed no statistical significant difference between the sensitivity and specificity of the methods.

Conclusions

We observed higher positive and lower negative likelihood ratios for relative ST analysis in comparison to absolute ST analysis. In this small study we found no statistical difference. Relative ST analysis should be studied in a larger study.

Introduction

To prevent neonatal asphyxia, clinicians need a reliable method for intrapartum fetal surveillance to intervene in time when necessary. Cardiotocography (CTG) has high sensitivity, but low specificity.[1] Additional techniques, such as fetal blood sampling or ST analysis, are used to improve specificity. The STAN method® (Neoventa, Mölndal, Sweden), using absolute ST waveform analysis, initially showed promising in terms of lowering asphyxia rates.[2] However, meta-analyses show inconclusive results regarding the effect of absolute ST analysis on cesarean section rates and fetal metabolic acidosis.[3] An explanation may be that the clinical relevance of these absolute ST events depends on CTG classification and that absolute ST events do not always reflect fetal distress.

ST analysis is based on the finding that hypoxia in fetal lambs is related to changes in the ST segment of the fetal electrocardiogram (fECG).[4] As a result, the STAN® method was developed for fetal surveillance during labor at term in humans. It generates three types of alarms if ST changes occur: episodic T/QRS rise, baseline T/QRS rise and biphasic events. Baseline and episodic events, which are based on T-top rises, are expressed as absolute rises in T/QRS ratio from baseline. Episodic events disappear within 10 min, while baseline events last for more than 10 min. Biphasic events, which are based on a negative slope of the ST segment, are reported to be related to acute stress and absent or exhausted compensation mechanisms.[5]

The clinical relevance of these ST events depends on CTG classification. The CTG is classified into four categories according to FIGO guidelines; ST events are defined as *significant* or not, depending on this CTG classification, following the STAN guidelines.[6,7] Kwee[8] showed that ST events occurred in more than 50% of normal CTG fragments during the first stage of labor and were evenly distributed in normal, intermediary and abnormal fragments in the second stage. These findings emphasize the fact that the STAN method® strongly depends on correct CTG interpretation, which is known to have high inter- and intraobserver variability.[9]

In previous studies we found a physiological explanation for these false positive absolute ST events and presented a solution: relative ST events (relative T/QRS rises from baseline).[10,11] We demonstrated that normal variations in the electrical heart axis between fetuses result in differences in the fetal vectorcardiogram, which yields different T/QRS baseline values. Moreover, we found that this T/QRS baseline value is positively related to the number of absolute ST events.[10] However, no association was found between T/QRS baseline value and neonatal outcome.[12]

We hypothesize that ST analysis can be improved if relative T/QRS rises (relative ST events) from baseline are used instead of absolute T/QRS rises (absolute ST events). This hypothesis applies to episodic and baseline ST events. Previously, we observed that relative events are more accurately related to fetal metabolic acidosis than absolute events. We found a specificity of 100% for the relative events versus 40% for the absolute events, with a sensitivity of 90% for both methods.[11] However, in the previous study we omitted CTG classification. As a result it was impossible to determine whether the absolute ST events were *significant* or not. In this study we compare diagnostic accuracy of relative ST events (new method) with *significant* absolute ST events (current method).

Materials and methods

Design & patients

We performed a case control study using the dataset collected by van Laar et al.[13] The cases (i.e. fetuses with acidemia) had a cord arterial pH below 7.05, whereas the controls (i.e. fetuses without acidemia) had a cord arterial pH above 7.20. The original study was approved by the medical commission of the Máxima Medical Center and conducted in accordance with the Declaration of Helsinki.[13]

Patients were retrospectively, consecutively, selected in two Dutch tertiary care teaching hospitals (University Medical Center Utrecht, UMCU Utrecht and Máxima Medical Center, MMC Veldhoven). Inclusion criteria were healthy women with healthy singleton fetuses of at least 36 weeks of gestation with good quality intrapartum fetal ECG recordings (no ectopic beats or missing data until at least 10 min before birth) and available arterial and venous acid base status from umbilical cord blood. Exclusion criteria were fetal growth restriction, fetal congenital anomalies, and use of medication other than oxytocin or epidural analgesia.

Data acquisition

Fetal ECG measurements were obtained during delivery with a single-helix scalp electrode (Goldtrace®, Neoventa Medical, Mölndal, Sweden), a maternal skin electrode and a STAN S31 monitor (Neoventa Medical, Mölndal, Sweden). We defined absolute events as episodic, baseline or biphasic ST events that were reported in the Event Log® by STAN®. Each up-to-20-min CTG recording preceding an absolute event was selected. Two obstetricians (>10 years experience) and STAN trainers (AK and MP) classified these CTG fragments as normal, intermediary, abnormal or preterminal following the FIGO guidelines.[6] Likewise, they classified each absolute ST

event as *significant* or *non-significant* based on the STAN guidelines. The reviewers were blinded to postpartum pH values. Discrepancies – regarding ST event classification - were resolved by discussion. A positive test for absolute ST analysis (STAN method®) was defined as at least one *significant* ST event per patient.

Our rationale and method of calculating the relative events has been described previously.[11] A positive test for relative ST-analysis (our method) was defined as a relative T/QRS rise from baseline above 70% at least once independent of CTG analysis. We chose this cut off value, since it delivered optimal accuracy in previous analysis.[11]

Statistical analysis

Test characteristics and 95% exact confidence intervals were calculated with Episheet © in Microsoft Excel 11.[14] SPSS Statistics version 22 was used for additional statistical analysis. To compare patient characteristics we used a Mann–Whitney U test for continuous variables and a Fisher's exact test for discrete variables. Test characteristics were compared using McNemar's test. The alpha level of .05 indicated statistical significance.

Results

In total 20 patients were included: 10 cases (umbilical artery pH value <7.05) and 10 controls (umbilical artery pH value >7.20). Baseline characteristics are shown in Table 1. Groups were similar in terms of parity, gestational age, and birth weight.

Table 1. Clinical characteristics and outcome parameters.

	pH < 7.05 (n = 10)	**pH > 7.20 (n = 10)**
Nulliparous	8 (80)	4 (40)
Gestational age – days	283 [8]	278 [11]
Analgesia	5 (50)	6 (60)
Oxytocin	7 (70)	4 (40)
FBS – frequency	**1.4 [1.3]**	**0**
Birth weight – gram	3414 [432]	3643 [562]
Apgar score after 1 min	**6 [2]**	**9 [1]**
Apgar score after 5 min	**8 [1]**	**10 [0]**
Cord arterial pH	**6.98 [0.07]**	**7.26 [0.03]**
Cord arterial base excess – mmol/l	**–17 [4]**	**–5 [2]**
Cord venous pH	**7.08 [0.10]**	**7.33 [0.04]**

Table 1. *(Continued)*

	pH < 7.05 (n = 10)	**pH > 7.20 (n = 10)**
Hospital admission	4 (40)	0 (0)
Medium Care	2 (20)	–
NICU	2 (20)	–
Operative delivery	4 (40)	(0)
Ventouse delivery	4 (40)	–
Cesarean section	0 (0)	–

The values are represented as number (%) or mean [standard deviation]. The values depicted in bold are significant using Fisher exact test in nominal variables and Mann–Whitney U test in continuous variables. FBS: fetal blood sampling; NICU: neonatal intensive care unit.

CTG and absolute ST event classification

In total 54 CTG fragments preceding absolute ST events were classified. AK and MP identically classified 85% of 54 CTG fragments. Discrepancies that led to different ST event classification were resolved by discussion. In the case group 29% of the 38 absolute ST events were significant; seven out of ten cases had at least one significant absolute ST event. In the control group, 19% of the 16 absolute ST events were significant; three out of ten controls had at least one significant ST event (Figure 1).

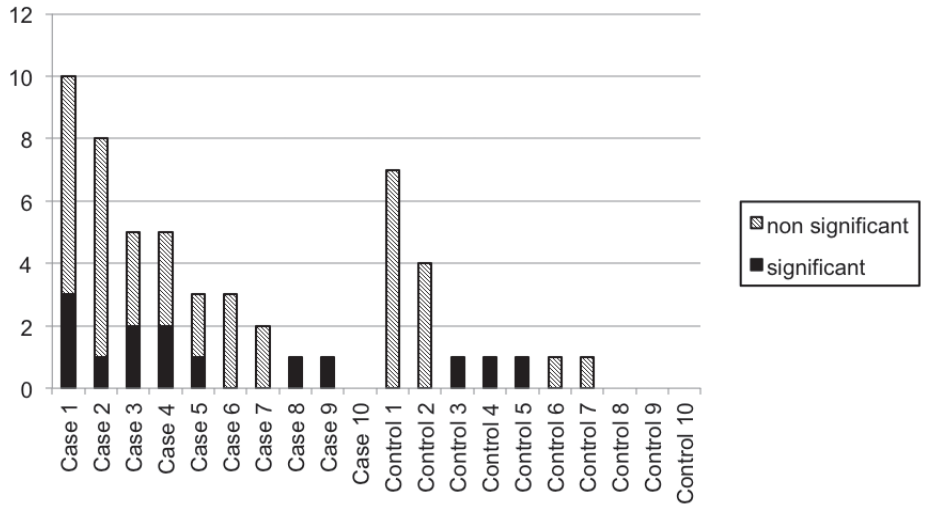

Figure 1. *Significant* absolute ST events per patient.

Figure 2 shows the distribution of absolute and relative ST events toward the time of delivery. The median time between the first event and birth was 14 min (ranging from 2 min after birth to 4 h and 38 min before birth) for *significant* absolute events and 4 h and 8 min (ranging from 11 min to 8 h and 7 min before birth) for relative events.

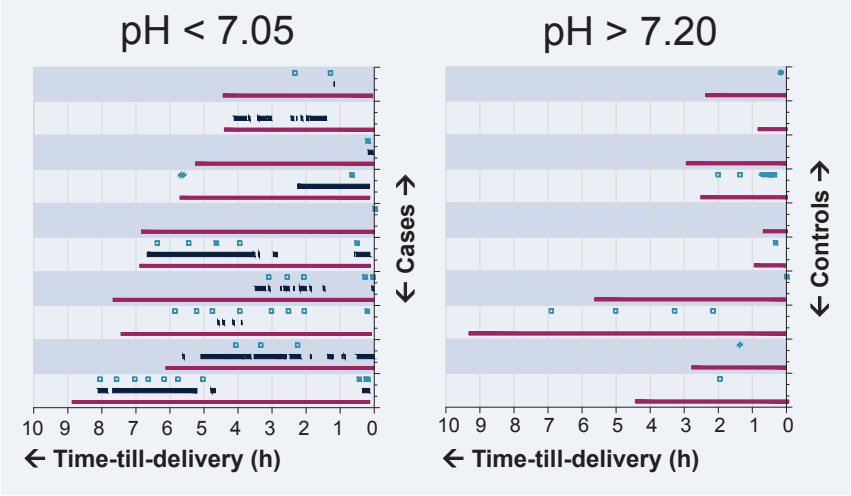

Figure 2. ST events and time-till-delivery. Pink bar, duration of measurement; navy bar, relative ST event (T/QRS rise from baseline >70%); blue dot (empty), non significant absolute ST events; blue dot (filled): significant absolute ST event.

Test characteristics

Test characteristics of absolute and relative ST analysis are shown in Table 2. Absolute ST analysis showed a sensitivity and a specificity of 70%. Relative ST analysis showed a sensitivity of 90% and a specificity of 100%. Both positive and negative likelihood ratios of absolute ST analysis indicated a small diagnostic effect, while the negative likelihood ratio of relative ST analysis indicated a moderate diagnostic effect. The positive likelihood ratio, the diagnostic odds ratio, and their confidence intervals could not be calculated for relative ST analysis as the specificity was 100%. These variables approximate to infinity.

Table 2. Test characteristics.

	Sensitivity (95%CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)	OR (95%CI)
Absolute ST analysis	70% (35–93)	70% (35–93)	2.3 (0.8–6.5)	0.4 (0.2–1.2)	5.4 (0.8–36.9)
Relative ST analysis	90% (55–100)	100% (69–100)	∞	0.1 (0.0–0.6)	∞

95%CI: 95% confidence intervals; LR+: positive likelihood ratio; LR-: negative likelihood ratio; OR: diagnostic odds ratio; ∞: infinity.

McNemar's test did not reveal significant differences between absolute and relative ST analysis regarding the true positives (p = 0.63) or the true negatives (p = 0.25).

Discussion

In this pilot study, we compared the diagnostic accuracy of absolute ST events (STAN method) and relative ST events with regard to fetal acidemia. We found a non-significant trend toward better test characteristics in relative ST analysis compared with absolute ST analysis. As confidence intervals of the positive likelihood ratio and diagnostic odds ratio of the relative method could not be determined, these variables could not be compared statistically to the absolute method. It seems that relative ST analysis is more promising for better diagnostic accuracy than absolute ST analysis, as these test characteristics approximate to infinity.

In a previous study, we found that the specificity of absolute ST-analysis was 40% in contrast to 70% in the current study.[11] The difference between these studies can be explained because CTG classification and biphasic ST events were not taken into consideration in the previous study. By using CTG classification many false positive absolute ST events can be ignored. It emphasizes how the STAN method® depends on correct CTG classification, which is a major drawback of absolute ST analysis. CTG interpretation, which is known to be subjective, has low-to-moderate inter- and intraobserver agreement.[9,15,16] The new method has shown better specificity as a stand-alone objective measurement of fetal well-being than the old one, as it does not depend on CTG interpretation.

Moreover, the value of a deteriorating CTG without ST events should not be underestimated. Another earlier described pitfall is that clinicians do not assess CTG continuously and feel "safe" as long as no ST event arises when the STAN method® is used in clinical practice. This way, slow CTG alterations (including baseline elevation or diminished variability) could be overlooked, resulting in adverse neonatal outcome.[15]

In three healthy control patients (pH >7.20) *significant* absolute ST events emerged. The time gap between event and delivery was less than 20 min. One event emerged within one minute after delivery. All these cases ended as a spontaneous vaginal delivery; no interventions that could improve postpartum pH, such as vacuum extraction or tocolytic agent, were used. This is why we can confirm that these cases are truly false positives of absolute ST analysis.

Biphasic ST events did not influence diagnostic accuracy in the current study, as none were *significant*. So far, we did not include biphasic events in relative ST analysis, as they are not influenced by T/QRS baseline and electrical heart axis. Besides, Becker et al.[17] showed that *significant* biphasic events do not have additional predictive value for fetal distress.

Remarkably, the sensitivity of absolute ST events with CTG information (70%) was lower than without CTG information (90%). These false negatives could be explained by CTG classification difficulties, even though experts classified the fragments. Suboptimal or abnormal CTG fragments could be classified as normal or suboptimal, which would change ST events to be classified as *significant* or *non-significant*.

A strength of this study is that two independent experienced obstetricians (>10 years experience) and STAN trainers classified the CTG fragments. They strongly agreed on the CTG classification. The test characteristics of the STAN method would probably be worse in clinical practice, as less experienced doctors and midwives will usually interpret the CTG in daily routine. Westerhuis has shown lower agreement on CTG classification among less experienced doctors and experts, than within a group of experts.[16]

We observed a large difference in the time-to-delivery interval from the first event between both methods. *Significant* absolute ST events probably led to clinical decisions to end delivery, which would explain the short median of 14 min. As this is a retrospective study, relative ST events were not available at the time of measurement, so they could not influence the clinical course. Relative ST events emerged earlier, which implies that relative ST analysis could predict metabolic acidosis at an earlier stage.

The physiological rationale for relative ST analysis

Each contraction of the heart is initiated by electrical potential propagation. The direction and the amplitude of the electrical potential change during the heart cycle; these factors depend on the direction of propagation (as different parts of the heart depolarize after each other) and the thickness of the muscular wall. The direction in which the electrical potential has maximal amplitude is called the electrical heart axis. If the fetal ECG signal is measured with a single electrode (scalp electrode), the amplitudes of the various ECG waves reflect the projection of the electrical potential in the direction of that – single – electrode. If the electrode is aligned in the same direction as the electrical heart axis, the largest ECG signal (largest amplitude) is measured. If the alignment differs, this influences the ECG amplitude. Since the

various waves in the ECG are not all parallel with the electrical heart axis, different waves are influenced to a different extent, causing changes in the ECG waveform. As a result, the alignment between the electrical heart axis and scalp electrode can influence ST events, regardless of fetal condition.

The current STAN method® normalizes the signal to address this problem; the T-top amplitude is normalized against the QRS complex as a T/QRS ratio. This method ignores the fact that the propagation direction in the depolarization phase (QRS) is not parallel (or antiparallel) to that in repolarization phase (T-top).

If the electrode alignment is almost perpendicular to the propagation during repolarization, a small T- wave arises. Hypoxia-induced T-wave changes will be small; they will not be detected as a substantial change. This leads to the false-negative absence of ST events. On the contrary, optimal alignment between the electrode and electrical heart axis leads to large amplitudes and thus larger T/QRS rises. The threshold to raise a ST event is exceeded more easily, even in normally oxygenated fetuses, which leads to false-positive ST events.

If events were raised based on a relative change from baseline instead of an absolute change, it would compensate for these inter-patient differences in electrical heart axis. Both false-positive and false-negative events will then be reduced.

Limitations

The limitations of this exploratory study are the small sample size and the contrasting groups (no complete spectrum of pH values). We chose this setup, as no previous research has been conducted on this subject yet. This way we could explore the new method as a proof of principle.

We found no significant differences in diagnostic accuracy. This could be explained by the small sample size.

Furthermore, relatively short CTG fragments preceding each ST event were available for CTG classification. We chose to present only 20-min fragments to the reviewers, since the STAN method® requires this minimum and the main CTG criteria can be determined (basal heart rate, accelerations, deceleration depth and duration, and variability). Besides, we wanted to ascertain optimal uniformity in the CTG length preceding each ST event.

Implications for further research

Relative ST analysis should be studied in a larger population with a complete spectrum of pH values. In such a large sample a new cut off for relative ST rises might be determined; consequently this new cutoff should be validated in an external dataset.

Registration of fECG was obtained with scalp electrodes in this study, whereas noninvasive abdominal registration might be used in future studies. If multiple abdominal electrodes are used, this will address the problem of electrical heart axis variation more specifically. Then the true electrical heart axis could be determined for each individual fetus. That way we could use an adjusted algorithm to calculate relative T/QRS rises, based on the individual angle between the electrode alignment and the fetal electrical heart axis. This would be a more specific solution than the general solution proposed in this study (relative T/QRS rises). This may improve the diagnostic accuracy of ST analysis even more. However, transabdominal fECG acquisition will pose new challenges, such as lower signal quality.[17]

In conclusion, relative ST events are promising to improve fetal monitoring during labor. This retrospective study showed a non-significant trend toward better diagnostic accuracy in relative ST analysis compared to absolute ST analysis (the current STAN method). More research should be conducted to determine the clinical value of this new method.

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CHAPTER 7

New possibilities for ST analysis – A post-hoc analysis on the Dutch STAN RCT

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Abstract

Background

The diagnostic value of ST analysis of the fetal electrocardiogram (fECG) during labor is uncertain. False alarms (ST events) may be explained by physiological variation of the fetal electrical heart axis. Adjusted ST events, based on a relative rather than an absolute rise from baseline, correct for this variation and may improve the diagnostic accuracy of ST analysis.

Aims

Determine the optimal cut-off for relative ST events in fECG to detect fetal metabolic acidosis.

Study design

Post-hoc analysis on fECG tracings from the Dutch STAN trial (STAN+CTG branch).

Subjects

1328 term singleton fetuses with scalp ECG tracing during labor, including 10 cases of metabolic acidosis.

Outcome measures

Cut-off value for relative ST events at the point closest to (0,1) in the receiver operating characteristic (ROC) curve with corresponding sensitivity and specificity.

Results

Relative baseline ST events had an optimal cut-off at an increment of 85% from baseline. Relative ST events had a sensitivity of 90% and specificity of 80%.

Conclusions

Adjusting the current definition of ST events may improve ST analysis, making it independent of CTG interpretation.

Introduction

ST analysis of the fetal electrocardiogram (fECG) seemed to be a very promising method for fetal monitoring during labor, as the technique would provide an objective addition to subjective fetal monitoring with cardiotocography (CTG).[1] However, multiple randomized controlled trials and meta-analyses showed contradictory results in fetal asphyxia or operative delivery rates when CTG was combined with ST analysis compared to solely CTG.[2-9]

The method of ST analysis combines CTG information with alarms (ST events) that arise in case of specific changes in the ST interval of the fECG during fetal hypoxia (Figure 1). ST analysis determines three types of ST events: episodic, baseline and biphasic ST events. Both episodic and baseline ST events reflect an absolute increase of the T/QRS value compared to a median T/QRS value in the preceding registration (the so-called T/QRS baseline). The combination of a suboptimal or abnormal CTG and one or more of these ST events, may reflect fetal hypoxia.

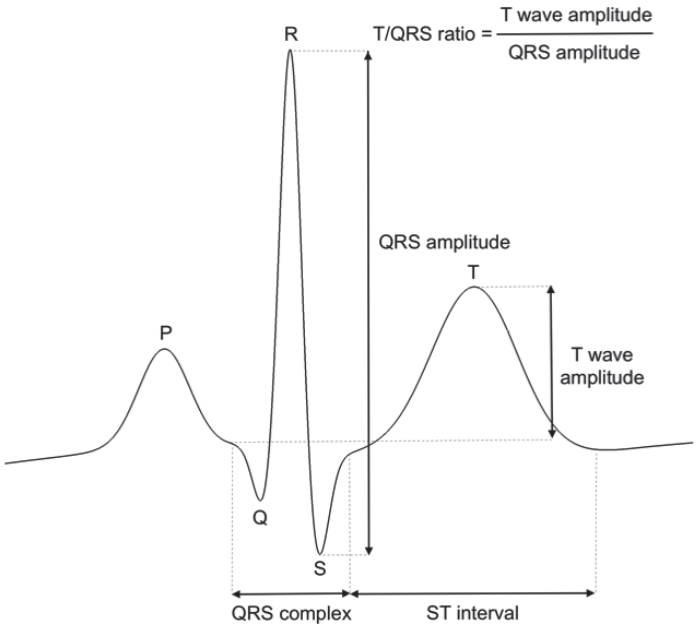

Figure 1. ECG parameters. The T/QRS value is the quotient of the T-wave amplitude and the QRS-amplitude.

However, Kwee et al. showed that ST events are also reported in 50% of normal CTG tracings.[10] Clinicians can ignore these ST events when they interpret the CTG as normal. CTG interpretation is known to be subjective and has a high intra- and inter-observer variability.[11,12] Therefore, ST events may potentially be erroneously interpreted. This might partly explain the disappointing results of ST analysis to detect metabolic acidosis or reduce operative delivery rates.[2-9] Adjusted ST alarms, independent from CTG interpretation, might improve the diagnostic accuracy of the ST analysis technique.

Becker et al. showed that the T/QRS baseline itself is independent of the fetal condition.[13] On the contrary, the T/QRS baseline depends on the position of the scalp electrode compared to the fetal electrical heart axis. As the fetal electrical heart axis varies between individuals and the fetal electrocardiogram is recorded from one single scalp electrode, this can influence fECG amplitudes and waveform.[14] In accordance to this, we found more ST events in fetuses with a higher T/QRS baseline.[15]

The current method of ST analysis does not take into account how the fetal electrical heart axis affects the amplitudes and waveform of the fECG. When the current definition is used, some fetuses are more prone to ST events than others, due to the alignment between the scalp electrode and the electrical heart axis regardless of fetal condition.[15]

Previously, we explored the value of adjusted ST events in a case controlled study.[16] These adjusted ST events were based on relative rises from T/QRS baseline – so-called 'relative' ST analysis. We found that the diagnostic accuracy of the adjusted ST analysis to detect an arterial cord pH <7.05 improved. Both sensitivity and specificity of relative ST events (without CTG) were higher compared to conventional ST analysis plus CTG (absolute ST analysis). However, this study was limited to two groups of fetuses, at the extremes of neonatal arterial cord pH; umbilical cord pH below 7.05 and above 7.20.

This study aims to determine the optimal cut-off for adjusted, so-called relative ST events in a cohort of fetuses within the full range of arterial cord pH values, in order to classify neonatal metabolic acidosis at birth.

Material and methods

We performed a post-hoc analysis on a prospectively collected cohort. Patients were included from the index group (CTG + ST analysis) from the Dutch STAN trial.[3] Inclusion criteria were women aged 18 years and older, during labor, pregnant of a singleton in cephalic position, with a gestational age above 36 weeks. We refer to the publication by Westerhuis et al.[3] for detailed information about the selected patients in the original trial. Additional exclusion criteria for the current study were: missing postpartum umbilical cord blood gas results, missing STAN tracings (Neoventa, Mölndal, Sweden), signal quality <50% in the last hour before birth, maternal fever during labor (>38 degrees Celsius), use of tocolytics, and fetal cardiac malformations or arrhythmia.

All patients in the CTG + ST arm of the original study were connected to a S21 or S31 STAN® monitor with a Goldtrace scalp electrode (Neoventa Medical, Mölndal, Sweden) applied to the fetal head. Both monitors used the same algorithm for ST analysis and stored the T/QRS values on the monitor. We extracted this original T/QRS information from the STAN® monitors. At first, we determined the medians of the T/QRS values in shifting windows of 10 and 20 min. Then, T/QRS baseline was defined the same way as in conventional ST analysis: the lowest median T/QRS value in a twenty-minute window in the registration up to maximally three hours ago. Additionally, we determined the T/QRS baseline without this three-hour restriction, including the entire registration done so far. Conventional ST analysis applies a restricted memory for three hours for the T/QRS baseline. We would argue that the baseline should be set at the best fetal condition, probably at the beginning of the measurement. This should logically not be restricted to the preceding three hours of registration. Therefore, we also examined the effect of ST events without the three-hour baseline memory restriction.

Finally, the relative differences between the T/QRS median and T/QRS baseline values were computed with Matlab2015b® (The Mathworks, Natick, MA). As such, we computed episodic as well as baseline relative ST events, in analogy of the conventional absolute episodic and baseline ST events. In conventional ST analysis, episodic events reflect a single T/QRS value that exceeds 0.10 compared to the median T/QRS value of the preceding 10 min. Conventional baseline events occur in case the median T/QRS value of the last 10 min exceeds at least 0.05 compared to the T/QRS baseline.

We explored two concepts for relative episodic and baseline ST events:

1) Episodic and baseline median length definitions with restricted baseline memory up to three hours. Relative episodic ST events represent the relative difference between the most recent T/QRS value and the median of T/QRS values over the last 10 min. Relative baseline ST events represent the difference between the median T/QRS values over the last 10 min compared to the T/QRS baseline (lowest 20 min median so far, restricted to last the three hours).

2) Episodic and baseline median length definitions with unrestricted baseline memory. In parallel with the previous concept, relative episodic ST events compare the most recent T/QRS value with the median T/QRS value over the last 10 min. Relative baseline ST events compare the median T/QRS value over the last 10 min with the T/QRS baseline (lowest 20 min median so far, since the start of the registration).

To determine sensitivity and specificity to detect metabolic acidosis for relative ST analysis, we defined a positive test for relative ST analysis as at least one relative ST event within the last hour before birth. Metabolic acidosis was defined as cord artery pH <7.05 and base deficit in the extracellular fluid (BD_{ecf}) >12 mmol/L directly after birth. The definition was set as pH <7.10 and BD_{ecf} >12 mmol/L in cases with only an umbilical vein sample (one available blood gas sample or the pH difference between two samples below 0.03).[17]

Clinical data were obtained from the original dataset of the Westerhuis trial[3]. In case variables were missing or unclear in the dataset, they were verified in the original patient files. Baseline characteristics were presented as medians with corresponding interquartile range (continuous variables) and number with corresponding percentage (categorical variables). The baseline characteristics were compared between the group with metabolic acidosis and the group without metabolic acidosis with a Mann-Whitney U test for continuous variables and a Fisher's exact test for categorical variables.

The aim of this study is to determine the optimal cut-off value for relative ST events and the corresponding sensitivity and specificity for metabolic acidosis. The above-mentioned definitions were used to calculate an area under receiver operator characteristic (ROC) curve (AUC) and to determine the cut-off value closest to (0,1) in this curve. The point closest to (0,1), defined as the minimum square of distance.

Besides, we performed a leave-one-positive-case-out cross validation, performing the same analysis for each metabolic acidosis patient: we defined the testing set as that single metabolic acidosis case, and the training set as all the rest (both metabolic acidosis and the other patients). We fitted the model on the training set, obtaining the optimal cut-off value and corresponding AUC. We then evaluated the diagnostic accuracy of each of the so-obtained 10 thresholds via sensitivity, specificity and diagnostic accuracy (percentage of correctly classified cases). All statistical analyses were performed in SPSS Statistics 22 for Mac (IBM, Armonk, NY).

Results

We included 1328 patients out of 2827 from the CTG + ST intention-to-treat branch from the Dutch STAN trial (Figure 2). Patient characteristics are presented in Table 1. The total duration of scalp ECG registration varied from 34 to 1352 min. In the group of cases with metabolic acidosis 3 (30%) registrations were shorter than 3 h, in the group without metabolic acidosis this was the case in 457 (34.7%) subjects.

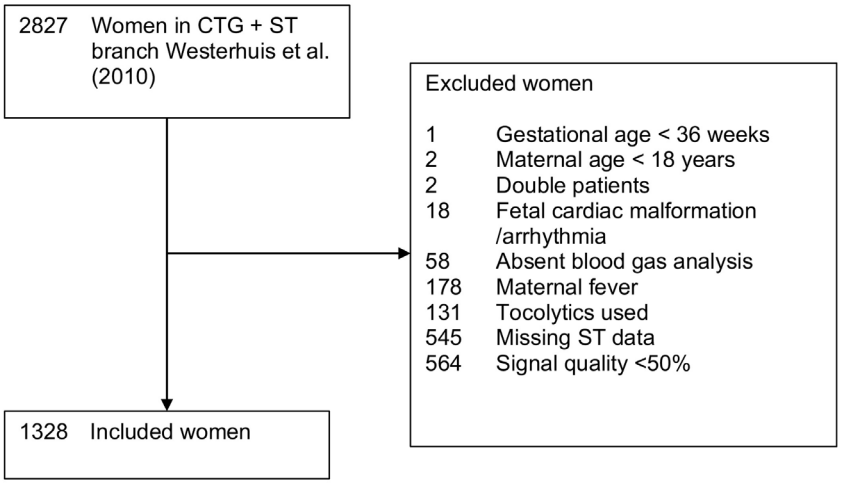

Figure 2. Flowchart of included and excluded patients.

Table 1. Patient characteristics of included women.

	Included women						
	Total (n = 1328)		Metabolic acidosis group (n = 10)		No metabolic acidosis group (n = 1318)		
	Median [IQR] or n (%)		Median [IQR] or n (%)		Median [IQR] or n (%)		p-value
Age at delivery - years	32.2	[28.9–35.3]	33.2	[28.0–38.9]	32.2	[28.9–35.3]	0.508
Nulliparous	722	(54.4)	7	(70.0)	715	(54.2)	0.361
Gestational age - days	282	[275–289]	283	[275–293]	282	[275–289]	0.600
Prolonged pregnancy >42 weeks	156	(11.7)	1	(10.0)	155	(11.8)	1.000
Birth weight - grams	3528	[3189–3870]	3635	[3198–4065]	3525	[3186–3870]	0.649
Small for gestational age (≤p10)	110	(8.3)	1	(10.0)	109	(8.3)	0.580
Fetal sex - male	724	(54.5)	5	(50.0)	719	(54.6)	1.000
Induction of labor	537	(40.4)	3	(30.0)	534	(40.5)	0.748
Epidural analgesia	481	(36.2)	5	(50.0)	476	(36.1)	0.510
Meconium stained amniotic fluid	326	(24.5)	3	(30.0)	323	(24.5)	0.714
Oxytocin augmentation	924	(69.6)	6	(60.0)	918	(69.7)	0.503
FBS	84	(6.3)	3	(30.0)	81	(6.1)	0.021
Cesarean section	35	(2.6)	1	(10.0)	34	(2.6)	0.235
Fetal distress	12	(34.3)	1	(100.0)	11	(32.4)	
Failure to progress	17	(48.6)	0	(0.0)	17	(50.0)	
Combination	4	(11.4)	0	(0.0)	4	(11.8)	
Other	2	(5.8)	0	(0.0)	2	(5.9)	
Instrumental vaginal delivery	159	(12)	6	(60.0)	153	(11.6)	<0.001
Fetal distress	77	(48.4)	6	(100.0)	71	(46.4)	

Table 1. *(Continued)*

	Included women						
	Total (n = 1328)		Metabolic acidosis group (n = 10)		No metabolic acidosis group (n = 1318)		
	Median [IQR] or n (%)		Median [IQR] or n (%)		Median [IQR] or n (%)		p-value
Failure to progress	68	(42.8)	0	(0.0)	68	(44.4)	
Combination	11	(6.9)	0	(0.0)	11	(7.2)	
Other	3	(1.9)	0	(0.0)	3	(2.0)	
Umbilical cord artery pH	7.22	[7.18–7.28]	7.02	[6.95–7.03]	7.23	[7.18–7.28]	<0.001
Apgar Score							
<4 at 1 min	17	(1.3)	4	(40.0)	13	(1.0)	<0.001
<7 at 5 min	14	(1.1)	4	(40.0)	10	(0.8)	<0.001
Hospital admission	129	(9.6)	5	(50.0)	124	(9.4)	0.001
NICU	11	(0.8)	1	(10.0)	10	(0.8)	0.080
Medium Care	118	(8.9)	4	(40.0)	114	(8.6)	0.008
HIE Sarnat 2 or 3 at discharge	0	(0)	0	(0)	0	(0)	–
Perinatal death	0	(0)	0	(0)	0	(0)	–

Metabolic acidosis was defined as cord artery pH <7.05 and base deficit in the extracellular fluid (BD_{ecf}) >12 mmol/L directly after birth. Abbreviations: FBS, fetal blood sampling; HIE, hypoxic ischemic encephalopathy; IQR, interquartile range; NICU, Neonatal Intensive Care Unit; SD, standard deviation. Groups were compared with Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables.

Table 2 shows AUC values for different relative ST events. Differences depend on event definition and memory restrictions. Relative episodic ST events were not statistically significant to detect metabolic acidosis; therefore we did not determine cut-off values for this type of events. Overall, ST events with unrestricted baseline memory had better AUC values compared to ST events with restricted memory. These differences were not statistically significant. Figure 3 shows the ROC curve for both relative ST events with and without memory restrictions.

Table 2. Diagnostic characteristics of both episodic and baseline relative ST events at optimal cut-off.

Relative ST event	Area under ROC curve	Cut-off	Sensitivity	Specificity
Episodic event, restricted memory	0.62 95%CI 0.47–0.76	[a]	[a]	[a]
Baseline event, restricted memory	0.82 95%CI 0.73–0.92	0.85	0.80 95%CI 0.44–0.97	0.86 95%CI 0.84–0.88
Episodic event, unrestricted memory	0.62 95%CI 0.47–0.76	[a]	[a]	[a]
Baseline event, unrestricted memory	0.85 95%CI 0.77–0.93	0.85	0.90 95%CI 0.56–1.00	0.80 95%CI 0.77 –0.82

[a] Not determined; 95%CI, 95% confidence interval.

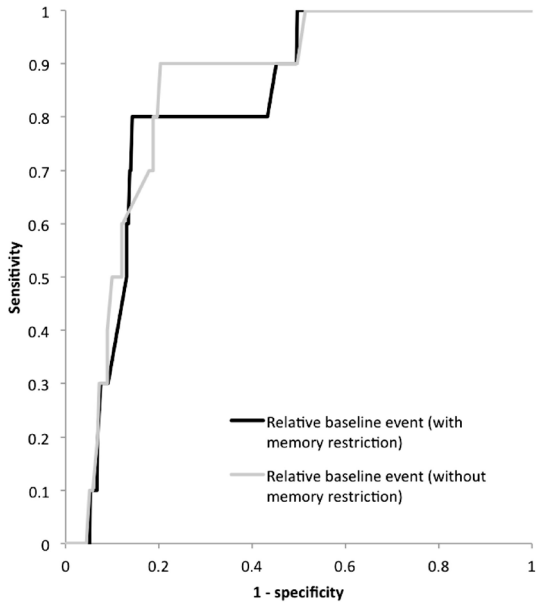

Figure 3. Receiver operating characteristic (ROC) curve of relative baseline ST events.

The optimal cut-off value of a relative baseline event with restricted memory based on the value closest to (0,1) was set at an increment of 85% from baseline. At this cut-off value, sensitivity was 80.0% and specificity was 85.7%. The optimal cut-off value for relative baseline ST events with unrestricted memory was also found at 85%, with a respective sensitivity of 90.0% and specificity of 79.7%.

To explore the classification performance of the relative baseline events within this dataset, we repeated the same analysis on the data leaving out one metabolic acidosis case at a time (n = 10). For events with restricted memory we found a mean sensitivity of 80.0% (range 77.8–88.9%), mean specificity of 85.8% (range 85.7–86.3%) in the training set, and a diagnostic accuracy of 80% in the testing set. For events with unrestricted memory we found a mean sensitivity of 90.0% (range 88.9–100.0%), mean specificity of 79.9% (range 79.7–81.2%) in the training set, and a diagnostic accuracy of 90% in the testing set. Details are presented in Tables S1 and S2 of the supplementary materials.

Discussion

We found that relative ST analysis has an area under the ROC curve of 0.85, with a sensitivity of 90%, and specificity of nearly 80% at the optimal cut-off value. In our previously published case control study, we found better diagnostic characteristics (AUC 0.99, sensitivity of 90% and specificity of 100%).[16] This may be explained by the fact that we omitted base deficit values for the determination of metabolic acidosis. Also, cases with mild acidosis (between pH 7.05 and 7.20) were excluded in this previous case control study. As a result, these more selected fetuses at the extremes of neonatal arterial cord pH are more likely to be correctly determined as healthy or compromised.

Test characteristics of our newly introduced relative ST analysis seem to be better than the current STAN method® (absolute ST analysis which includes CTG classification). Amer-Wåhlin et al. reported a sensitivity of 0.63 and a specificity of 0.66 of significant ST events.[18] Furthermore, the new relative ST analysis is independent of CTG interpretation, which is known for its high intra- and inter-observer variability.[12,19]

Besides changing the ST event definition from an absolute to a relative rise from baseline, we examined ST events that omit the T/QRS baseline reset after three hours. In the original STAN method® the last 10 min over the lowest 20 min in the last three hours of a recording are used. In the current study, we used the lowest

baseline T/QRS value of the individual fetus as a reference without the three hour restriction. Assuming that fetal condition will most likely worsen during labor, the lowest T/QRS value represents the most optimal fetal condition. It is unclear why the reference is adjusted every three hours in the original STAN method.

We chose to use the registration from the last hour before time of birth, to ascertain the relation between T/QRS value and metabolic acidosis (the closest moment between the ECG and a reliable marker of neonatal wellbeing). In theory, an early event could indicate fetal compromise, which returned to a normal condition after successful interventions, such as stopping oxytocin infusion. As this is a retrospective study, no clinical decisions could have been made on potential relative ST events. Therefore, when examining the total time of registration instead of mere the last hour of registration, the relation between ST events and metabolic acidosis would be less reliable.

The here presented test characteristics for relative ST events only reflect an estimation of the sensitivity and specificity of metabolic acidosis as no actual clinical decision was made on these relative ST events. The limited amount of cases of metabolic acidosis resulted in wide confidence intervals of the test characteristics. Partial cross validation leaving-one-metabolic-acidosis-case-out shows comparable diagnostic accuracy. In future studies, the cut-off should be externally validated in a population with comparable clinical characteristics and high quality fECG tracings.

In conclusion, revision of the current definition of ST events may improve ST analysis of the fECG. Relative ST analysis may provide a method that is independent of CTG interpretation. If so, it thereby expands more objective methods for fetal monitoring. Before this method could be implemented, relative ST analysis needs external validation.

Supplementary materials

The supplementary materials contain the following two tables and can be accessed via the link presented below:

- **Table S1.** Diagnostic characteristics of relative baseline events with restricted memory leaving one metabolic acidosis case out.
- **Table S2.** Diagnostic characteristics of relative baseline events with unrestricted memory leaving one metabolic acidosis case out.

https://ars.els-cdn.com/content/image/1-s2.0-S037837822100236X-mmc1.docx

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CHAPTER 8

General discussion

This thesis describes fetal electrocardiography (ECG) during labor as a method to monitor fetal well-being. The main focus is ST analysis (the STAN method) of the fetal ECG. The STAN method generates ST alarms based on fetal ECG waveform changes in the ST segment of the fetal ECG. As described in Chapter 1 the value of STAN to lower asphyxia and cesarean section rates is under debate. In part this may be explained by the major limitation that the method depends on (subjective) interpretation of the cardiotocogram (CTG).

We hypothesized that the STAN method can generate "false" alarms due to physiological influences: normal variation of the electrical heart axis and the alignment between the electrical heart axis and the electrode (Chapters 2-4). Besides, we explored whether it is feasible to correct for these effects with a new type of alarms: relative ST alarms (Chapters 5, 6 and 7).

This chapter will discuss the main findings, limitations, implications and future perspectives of the initially formulated questions:

1. *Does the fetal electrical heart axis vary between fetuses during mid-term pregnancy?*

It is known that the electrical heart axis varies between individuals in term fetuses, neonates and adults.[1-4] Chapter 2 describes our prospective cohort study, which explores the distribution of the electrical heart axis in fetuses in mid-term pregnancy of 25 women between 18+1 and 28+2 weeks of gestation. The dominant observed electrical heart axis was towards the right-posterior-inferior direction. The variation of the electrical heart axis between these individuals varied significantly compared to a normal distribution (p=0.016). We can conclude that the fetal electrical heart axis varies between individuals during mid-term pregnancy. These findings are in line with the known variation in older individuals. As the alignment between the electrode and the electrical heart axis determines the amplitude of the ECG waveform, we hypothesized that this alignment – that varies between patients because of the variation in the orientation of the electrical heart axis – could influence the interpretation of fetal ECG waveform variables (such as T/QRS ratios in the STAN method).

2. *What is the relation between T/QRS baseline value and the diagnostic accuracy of ST analysis?*

Kwee et al. reported that ST alarms occur in approximately 50% of all registrations during the first stage of labour and that ST alarms are equally encountered in both

normal as in abnormal CTG tracings.[5] We suggest a possible explanation for these false positive ST alarms in Chapter 3.

Each heart contraction is initiated by propagation of an electrical potential. During each heart cycle the direction and the amplitude of the electrical potential change, as different parts of the heart depolarize after each other and the thickness of the muscular wall varies in the heart. The direction in which the electrical potential has maximal amplitude is called the electrical heart axis. In the STAN method, the fetal ECG signal is measured with a single electrode on the scalp. That single electrode reflects the amplitudes of the various ECG waves in the direction of that electrode. The more the electrode is aligned in the same direction as the electrical heart axis, the larger the measured ECG signal (amplitude) is. As the various ECG waves are not all parallel with the electrical heart axis, different waves are influenced to a different extent, depending on the alignment between the electrode and the electrical heart axis, causing changes in the ECG waveform.

As the alignment between the electrical heart axis and the fetal scalp electrode influences fetal ECG waveform amplitudes, we hypothesize that this effect will also influence the parameter used for ST alarms: the T/QRS value. When the direction of the T-wave is more aligned with the electrical heart axis and the scalp electrode, we would expect higher T-wave amplitudes, resulting in higher T/QRS ratios and thus a higher initial T/QRS baseline value. When glycogenolysis during asphyxia influences the T-wave, a more aligned T-wave would be reflected as a higher T/QRS change than a less aligned T-wave. We hypothesized that fetuses with a higher initial T/QRS baseline would show more ST alarms than fetuses with a lower initial T/QRS baseline, as ST alarms are based on a fixed absolute rise of the T/QRS value from the T/QRS baseline.

In a post-hoc analysis of 1097 fetal ECG registrations from the Dutch STAN trial of fetuses born without metabolic acidosis, we compared the amount of ST alarms between fetuses depending on their initial T/QRS baseline value. We observed a significant increment of ST alarms with increasing height of the initial T/QRS baseline, irrespective of the fetal condition (correlation coefficient 0.63, $p<0.001$). The results showed an average increment of 1.42 ST alarms per 1000 T/QRS values for a rise of 0.1 of the initial baseline T/QRS. Our finding that the height of the initial baseline had no relation to the fetal condition is in line with Becker et al.[6] who reported that initial T/QRS baseline does not predict adverse neonatal outcome nor interventions for suspected fetal distress.

We concluded that the results of this study support our hypothesis. Some fetuses (with a high initial T/QRS baseline) have a relatively high probability of getting ST alarms and some fetuses (with a low initial T/QRS baseline) have a relatively low probability, irrespective of their condition. When using the STAN method in clinical practice, clinicians should be aware of this limitation.

We further hypothesize that ST analysis based on relative rather than absolute elevations of the T/QRS ratio compared to the initial baseline could correct for this effect. This will be discussed in the answer to question 4 in this Chapter.

3. *What is the relation between head orientation and electrode position on scalp ECG waveform?*

In adult ECG registrations multiple electrodes positioned at different positions on the body (4 extremity electrodes and 6 chest electrodes) result in a 12-lead ECG.[7] Every lead represents the electrical activity from the heart in the direction between two electrodes (bipolar lead) or towards one electrode compared to the combination of the other electrodes (unipolar lead). All 12 leads together can be considered to represent a 3D representation of the electrical activity of the heart. The amplitudes of the ECG waveform vary between leads, as the alignment of the different electrodes and the electrical heart axis differs. To correctly interpret ECG waveform, the information of the combined leads is essential. In fetal ECG with the STAN method, the ECG is measured from a single unipolar electrode on the fetal scalp.[8] The electrode is placed at the available position on the scalp after sufficient dilation of the cervix. The alignment between this electrode and the electrical heart axis is unknown.

Another difference with adult ECG registrations, is that the fetus is surrounded by conductive media (such as amniotic fluid and maternal tissue). The orientation between the fetal head and the fetal rump changes during labor. We hypothesized that the ECG waveform does not remain equal when it is measured with a unipolar scalp electrode in different orientations of the head and is surrounded by conductive media. Therefore, we tested our hypothesis in an experimental setting in one adult subject in both dry and immersed conditions, with electrodes at different positions on the head and in different orientations between the head and rump (Chapter 4).

In the dry condition in unipolar leads, we observed a stable ECG waveform. In dry conditions, cardiac currents are solely conducted through the body from the heart to the electrode at the scalp. The scalp can be regarded as the extension of the

neck, thus all electrode positions on the head reflect the same lead. Even a changed orientation of the head compared to the rump (e.g., bending of the neck), would not change the path of the cardiac currents.

In the immersed condition, we observed different ECG waveforms for the various electrode positions on the scalp and various head orientations. We found that different head rotations lead to different T/QRS values. We also found that the T/QRS value differs between electrode locations. The differences can be explained as the electrical currents generated by the heart propagate to the scalp electrode both intracorporally and extracorporally (i.e., through the conductive saline medium). The path of extracorporal conduction depends on the distance, position and presence of conductive media between the electrode and the heart, which varies for different electrode positions and head orientations.

These findings are partly in line with the study by Lindecrantz et. al.[9], who compared fetal ECG morphology in both bipolar and unipolar leads in a fetal lamb. They found that the bipolar scalp ECG inverts due to the rotation of the fetal head in the birth canal.[9] In that study, the unipolar ECG waveform remained stable after head rotation, therefore, they concluded that unipolar ECG is suitable for fetal monitoring.

If our experimental setup is comparable to the condition of a fetus during labor, this would implicate that both the position of the electrode on the fetal scalp and the orientation of the fetal head towards the rump (e.g., during the rotation in the birth canal) could influence T/QRS values and thus influence the amount of (both absolute and relative) ST alarms in ST analysis. In fact, a different position of the electrode on the scalp could lead to a different T/QRS baseline. As we found in Chapter 3, this different baseline could affect the incidence of ST alarms. This experiment implies that intrapartum fetal monitoring based on ECG waveform obtained by a single scalp electrode might be suboptimal, as there is no correction for neither fetal head orientation nor electrode position.

This study has some limitations, which imply that extrapolating results to the fetal situation should be done with caution. At first, the experiment was conducted only twice in one individual. We observed ECG changes in the immersed condition, but the size of these changes was inconsistent between both measurements. This could be explained by different conditions over time, although we attempted to minimize these effects. This experiment should be repeated multiple times in different individuals to enable a more quantitative analysis of ECG waveform changes.

Secondly, the setup of this experiment is a simplified environment compared to the fetal condition during labor. To examine the effect of surrounding (maternal) tissues on the waveform of the fetal scalp ECG in clinical practice would require comprehensive denotation or correction of the scalp electrode position and fetal head orientation during all stages of labor. This seems practically unfeasible. However, clinicians should be aware that fetal condition is not the only factor influencing the waveform of the fetal scalp ECG.

4. *Can the diagnostic accuracy of ST analysis be improved by relative ST alarms (correcting for initial T/QRS baseline)?*

As described before (question 2), the orientation between the electrical heart axis and the scalp electrode influences the ECG waveform. The current STAN method addresses this problem by normalizing the T-top amplitude against the QRS-complex as a T/QRS ratio. It does not take into account that the propagation direction in the depolarization phase (QRS) is not parallel to that in the repolarization phase (T-top). This may lead to erroneous ST alarms, when a T/QRS rise only triggers an alarm in case that a fixed absolute threshold is exceeded.

If the electrode alignment is almost perpendicular to the propagation during repolarization, a small T-wave arises and hypoxia-induced T-wave changes will be small in the measured ECG. The absolute threshold for T/QRS rise will not be exceeded and may lead to the false-negative absence of ST alarms. On the contrary, optimal alignment between the electrode and electrical heart axis leads to large amplitudes and thus larger T/QRS rises. The threshold to raise a ST alarm is more easily exceeded, even in normally oxygenated fetuses, which may lead to false-positive ST alarms.

We propose to raise ST alarms based on a relative change from baseline (relative ST alarms) instead of an absolute change (absolute ST alarms, i.e., conventional episodic and baseline ST events). This would correct for individual differences in electrical heart axis and the alignment between the electrode and the electrical heart axis.

Chapters 5 and 6 describe two retrospective case-control pilot studies that explored whether adjusted ST events (relative ST alarms), based on a relative rather than an absolute rise from T/QRS baseline, may improve the diagnostic accuracy of ST analysis. The first study omits CTG classification and biphasic ST alarms, the second study includes both CTG classification and biphasic ST alarms for the conventional (absolute) STAN method. We compared scalp fetal ECG tracings of 10 cases (fetuses with acidemia at birth) and 10 controls (fetuses without acidemia at birth).

The results showed that relative ST alarms are promising to improve the STAN method. Relative ST analysis showed an area under the ROC curve of 0.99 at a relative T/QRS rise from baseline of 70%. Relative versus absolute ST analysis showed significantly better specificity (100% vs 40%) at comparable sensitivity (90% vs 90%).

When clinical interpretation of the CTG was included for absolute ST analysis, we found a non-significant trend in favor of relative ST alarms; specificity (100% vs 70%) and sensitivity (90% vs 70%). None of the biphasic ST alarms were classified as significant, and did therefore not influence the diagnostic accuracy of absolute ST analysis.

The higher specificity of the absolute STAN method in the second study compared to the first study can be explained by the fact that "false positive" absolute ST alarms can be ignored when the CTG is classified as normal, which improves specificity of the absolute method. It emphasizes how the absolute STAN method depends on correct CTG classification, which is known to be subjective and has low-to-moderate inter- and intraobserver agreement.[10-12] In these studies, the relative method has shown equal and better specificity as a stand-alone method without CTG interpretation. Fewer unnecessary (false) alarms may diminish alarm fatigue by the health care providers.

We observed a shorter time-to-delivery interval from the first ST alarm in absolute ST analysis compared to the first ST alarm in relative ST analysis. Significant absolute ST alarms probably led to clinical decisions to end delivery. As the case-control study had a retrospective setup, relative ST alarms were not available at the time of measurement, and could not influence the clinical course. Relative ST alarms emerged earlier, which may imply that relative ST analysis could detect metabolic acidosis in an earlier stage.

The limitations of these pilot studies are the small sample size and the contrasting groups (lacking the complete spectrum of pH values). We chose this setup, to explore the new alarms as a proof of principle, as no previous research had been conducted on this subject by then. The small sample size may explain why no statistical differences were found in the second study. A large middle group with umbilical cord pH between 7.05 and 7.20 was not represented, which makes the studies not comparable to clinical practice. The results of these studies should therefore be interpreted with caution.

After the promising results from Chapters 5 and 6, we set up a larger study with the complete spectrum of pH values to determine a more representative cut-off value for relative ST alarms (Chapter 7). A post-hoc analysis followed on 1328 intrapartum scalp fetal ECG tracings from the Dutch STAN trial which included 10 cases of metabolic acidosis. We found the optimal cut-off for relative baseline ST alarms at an increment of 85% from baseline. Relative ST alarms had a sensitivity of 90% and specificity of 80% to detect fetal metabolic acidosis, the area under the ROC curve was 0.85. These test characteristics for relative ST alarms only reflect an estimation of the sensitivity and specificity to detect metabolic acidosis as no actual clinical decisions could have been made based on these relative ST alarms. The limited number of cases of metabolic acidosis resulted in wide confidence intervals.

The test characteristics for relative ST alarms were lower in the post-hoc analysis (Chapter 7) than those in the case-control pilot study (Chapter 5). We expected this difference, as fetuses at the extremes of neonatal arterial cord pH (either pH >7.20 or pH <7.05) are more likely to be correctly determined as healthy or compromised than cases with milder compromise. Nevertheless, the test characteristics of relative ST analysis seem to be better than the current STAN method (absolute ST analysis which includes CTG classification); Amer-Wåhlin et al.[13] reported a sensitivity of 0.63 and a specificity of 0.66 for significant absolute ST alarms to detect metabolic acidemia and 0.56 respectively 0.92 when significant absolute ST alarms were combined with CTG classification.

In the conventional STAN method T/QRS changes are compared to the so-called T/QRS baseline. After the first 20 minutes of the registration this initial T/QRS baseline value is set and automatically updated after three hours or in case a lower T/QRS baseline value is detected. Assuming that fetal condition will most likely worsen during labor, the lowest T/QRS value represents the most optimal fetal condition. The rationale behind the reset after three hours is unknown. Therefore, we presented the adjusted relative ST alarms both with and without time restriction.

We suggest that future studies should externally validate the cut-off for relative ST alarms in a population with comparable clinical characteristics and high-quality fetal ECG tracings. Unfortunately, there is a lack of available large datasets with high quality raw fetal ECG data stored electronically, accompanied by complete and relevant clinical information. This delays further progress in this field of research. After external validation, a prospective cohort study should follow to evaluate this method in clinical practice.

Another suggestion for future research is replacing the invasive single scalp electrode by multiple non-invasive electrodes on the maternal abdomen. Lempersz et al. and Vullings et al.[14-16] showed that it is feasible to extract a 12-lead fetal ECG with this method (offline processing) and to perform real-time RR-interval recording during labour. A real-time registration that combines multiple electrodes could more specifically address the problem of electrical heart axis variation. The actual electrical heart axis could be determined and used in an algorithm to calculate relative T/QRS rises, based on the individual angle between the electrode alignment and the fetal electrical heart axis. This may improve the diagnostic accuracy of ST analysis even more. However, transabdominal fetal ECG acquisition does need to conquer challenges such as low signal quality and changes in the ECG due to fetal movement. Unlike in registrations with the scalp electrode, the orientation between the fetus and the transabdominal electrodes can change with fetal movement in registrations with the non-invasive ECG technology.[17] ECG changes due to movement must therefore be distinguished from ECG changes due to hypoxia.

The value of a deteriorating CTG without ST alarms (absolute or relative) should not be underestimated. Even if relative ST analysis will improve diagnostic accuracy of the STAN method, CTG classification cannot be totally abandoned as it provides different information of the fetal well-being. A pitfall of not assessing the CTG and feeling "safe" as long as no ST alarm arises, can be that slow CTG alterations are overlooked (including fetal heart rate baseline elevation or diminished variability), resulting in adverse neonatal outcome.[11]

In conclusion, revision of the current definition of ST alarms may improve ST analysis of the fetal ECG. Relative ST analysis may provide a method with alarms independent of CTG interpretation. If so, it thereby adds an objective method for fetal monitoring.

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CHAPTER 9

English summary

Reliable fetal monitoring during labor is essential to reduce perinatal morbidity and mortality. Fetal electrocardiography (ECG) waveform interpretation is one of the tools that can be used during labor to assess fetal well-being or distress. ST analysis (the STAN method) generates ST alarms based on fetal ECG waveform changes in the ST segment of the fetal ECG. However, its value to reduce perinatal asphyxia and cesarean section rates is under debate. Besides, guidelines stipulate that the management of labour should not be based on ST analysis alone, but should also depend on the correct interpretation of the cardiotocogram (CTG). Chapter 1 describes the physiology of fetal circulation and currently available monitoring technologies. We hypothesize that false alarms in the conventional method of ST analysis are influenced by physiological variations of the fetal electrical heart axis and the alignment between the fetal scalp electrode and this fetal electrical heart axis (Chapters 2, 3 and 4). Furthermore, we explore whether adjusting ST alarms to relative ST alarms could correct for these effects (Chapters 5, 6 and 7).

Chapter 2 describes the distribution of the fetal electrical heart axis in 25 healthy women in mid-term singleton pregnancy. In this prospective cohort study, we found that the fetal electrical heart axis varies between individuals, just like in neonates and adults. The dominant observed orientation of the fetal electrical heart axis was towards the right-posterior-inferior octant.

Chapter 3 describes a post-hoc analysis on 1097 patients from a multicenter randomized controlled trial monitored with ST analysis during labor. We aimed to evaluate the relation between the physiological variations of the fetal electrical heart axis and the occurrence of ST alarms. We used the initial T/QRS baseline value as a parameter reflecting the orientation of the fetal electrical heart axis. We found that fetuses with higher initial T/QRS baseline showed significantly more ST alarms during the registration than fetuses with a lower initial T/QRS baseline, irrespective of the fetal condition. The effect of the individual fetal electrical heart axis on ECG waveform should be considered, when fetal ECG waveform is interpreted in ST analysis.

Chapter 4 describes a study that explored the influence of electrode position and head orientation on ECG waveform in air and in a conductive medium. We recorded ECGs at 5 different scalp positions in one adult subject in different head orientations in dry and immersed conditions. We found that both unipolar and bipolar scalp lead-derived ECG waveforms are influenced by electrode position and head orientation when the subject is submerged in a conductive medium. This may imply that fetal monitoring based on single scalp lead ECG waveform might be suboptimal, as it lacks correction for fetal head orientation and electrode position.

Chapters 5 and 6 describe two retrospective case-control studies that explored whether adjusted ST alarms, based on a relative rather than an absolute rise from T/QRS baseline, correct for variations in the electrical heart axis, variations in the head orientation and electrode position and may improve the diagnostic accuracy of ST analysis. We compared scalp fetal ECG tracings of 10 cases (fetuses with acidemia at birth) and 10 controls (fetuses without acidemia at birth). Relative ST analysis showed an area under the ROC curve of 0.99. Relative versus absolute ST analysis showed significantly better specificity (100% vs 40%) at comparable sensitivity (90% vs 90%). When clinical interpretation of the CTG was included for absolute ST analysis, we found a trend in favor of relative ST alarms; specificity (100% vs 70%) and sensitivity (90% vs 70%).

Chapter 7 describes a post-hoc analysis on 1328 intrapartum scalp fetal ECG tracings from the Dutch STAN trial. We compared relative ST values between cases with and without metabolic acidosis to determine an optimal cut-off for relative ST alarms. CTG classification was not taken into account. We found the optimal cut-off for relative baseline ST alarms at an increment of 85% from baseline. In this study relative ST alarms had a sensitivity of 90% and specificity of 80% to detect fetal metabolic acidosis (fetal distress), the area under the ROC curve was 0.85. This study suggests adjusting the current definition of ST alarms can improve diagnostic accuracy of ST analysis and might make it independent of CTG interpretation.

CHAPTER 10

Nederlandse samenvatting

Betrouwbare foetale bewaking tijdens de bevalling is essentieel om de perinatale morbiditeit en mortaliteit te verminderen. ST-analyse (STAN methode) van het foetale elektrocardiogram (ECG) is een methode die tijdens de bevalling gebruikt kan worden om de conditie van het ongeboren kind te beoordelen. Het foetale ECG wordt geregistreerd met een electrode op het hoofd van het kind. Als er bepaalde veranderingen optreden in de vorm van het ST-segment van het foetale ECG die wijzen op zuurstoftekort bij de foetus, genereert de STAN methode zogenaamde ST-alarmen. Er kleven enkele nadelen aan deze technologie. De STAN methode geeft regelmatig ST-alarmen, terwijl de conditie van het kind toch goed is. Daarnaast staat ter discussie of deze technologie daadwerkelijk perinatale asfyxie en het aantal keizersneden vermindert. Bovendien kan de STAN methode volgens de geldende richtlijnen alleen gebruikt worden in combinatie met het cardiotocogram (CTG), een subjectieve beoordeling van het hartritme.

De hypothese van dit proefschrift is dat de huidige STAN methode valse alarmen genereert door invloeden die onafhankelijk zijn van de conditie van de foetus. Enerzijds is dit de normale variatie van de foetale elektrische hartas tussen individuen. Anderzijds is dit de positie van de elektrode op het hoofd van het kind ten opzichte van de foetale elektrische hartas. Verder onderzoeken we of we voor deze effecten kunnen corrigeren met aangepaste ST-alarmen (relatieve ST-alarmen).

Hoofdstuk 2 beschrijft de verdeling van de foetale elektrische hartas bij 25 gezonde zwangeren in het tweede trimester of vroeg in het derde trimester. In deze prospectieve cohortstudie ontdekten we dat de foetale elektrische hartas varieert tussen individuen, net als bij pasgeborenen en volwassenen. De dominante richting van de foetale elektrische hartas was naar rechts-achter-onder.

Hoofdstuk 3 beschrijft een post-hoc analyse van 1097 patiënten uit een multicenter gerandomiseerde gecontroleerde studie, die gemonitord werden met de STAN methode tijdens de bevalling. Het doel van de studie was om de relatie te evalueren tussen de normale variaties van de foetale elektrische hartas en het optreden van ST-alarmen. We gebruikten de initiële T/QRS-basislijn als parameter voor de oriëntatie van de foetale elektrische hartas. We vonden dat foetussen met een hogere initiële T/QRS basislijn significant meer ST alarmen vertoonden dan foetussen met een lagere initiële T/QRS baseline, ongeacht de foetale conditie. We concludeerden dat er rekening moet worden gehouden met de individuele elektrische hartas van het ongeboren kind bij het interpreteren van de vorm van het foetale ECG, zoals bij de STAN methode.

Hoofdstuk 4 beschrijft een studie die onderzoekt of en hoe de vorm van het ECG verandert afhankelijk van de positie van de elektrode op het hoofd en de houding van het hoofd ten opzichte van de romp. Dit werd onderzocht bij een gezonde volwassene in zowel een droge conditie (lucht) als een natte conditie (ondergedompeld in een geleidend medium, een zoutwaterbad). Het ECG werd geregistreerd vanuit 5 verschillende hoofdhuidposities bij één volwassen proefpersoon tijdens verschillende houdingen van het hoofd. We ontdekten dat, in de natte conditie, de vorm van het ECG in zowel unipolaire als bipolaire metingen werd beïnvloed door zowel de positie van de elektroden als de houding van het hoofd. Dit zou kunnen betekenen dat foetale bewaking op basis van ECG-vormanalyse gebaseerd op één schedelafleiding niet optimaal is. Hierbij wordt namelijk niet gecorrigeerd voor de positie van het hoofd van de foetus, noch voor de positie van de elektrode.

Hoofdstukken 5 en 6 beschrijven twee retrospectieve case-control studies die onderzochten of gecorrigeerde ST-alarmen, gebaseerd op een relatieve in plaats van een absolute stijging vanaf de T/QRS-basislijn, de diagnostische nauwkeurigheid van ST-analyse kunnen verbeteren. We vergeleken foetale ECG-registraties van 10 "zieke" kinderen (foetussen met zuurstoftekort bij de geboorte) en 10 "gezonde" kinderen (foetussen zonder zuurstoftekort bij de geboorte). Het ideale afkappunt voor relatieve ST alarmen lag bij een stijging van 70% ten op zichte van de basislijn en toonde een oppervlakte onder de ROC-curve van 0,99. Relatieve versus absolute ST-analyse toonde een significant betere specificiteit (100% versus 40%) bij vergelijkbare sensitiviteit (90% versus 90%). In de tweede studie werd de CTG-beoordeling meegenomen voor absolute ST-analyse (reguliere STAN methode). In die studie vonden we een trend in het voordeel van relatieve ST-alarmen; specificiteit (100% vs. 70%) en sensitiviteit (90% vs. 70%).

Hoofdstuk 7 beschrijft een post-hoc analyse van 1328 intrapartum foetale ECG-registraties uit de Nederlandse STAN trial. We bepaalden de optimale afkapwaarde voor relatieve ST-alarmen door relatieve ST-waarden te vergelijken van kinderen met en zonder metabole acidose. CTG-beoordeling werd buiten beschouwing gelaten. De optimale afkapwaarde voor relatieve baseline ST-alarmen lag bij een stijging van 85% vanaf de basislijn. In deze studie hadden relatieve ST-alarmen een sensitiviteit van 90% en een specificiteit van 80% om foetale metabole acidose (foetale nood) te detecteren, de oppervlakte onder de ROC-curve was 0,85. Op basis van deze studie stellen wij voor om de huidige definitie van ST-alarmen aan te passen naar relatieve ST-alarmen om de diagnostische nauwkeurigheid van ST-analyse te verbeteren. Dit zou de methode onafhankelijk kunnen maken van CTG-beoordeling.

APPENDICES

List of abbreviations

List of publications

Dankwoord

Curriculum Vitae

List of abbreviations

95% CI	95% confidence interval
ASTAN	Absolute ST analysis
AUC	Area under the curve
AV node	Atrioventricular node
BD_{ecf}	Base deficit in the extracellular fluid
BMI	Body Mass Index
CTG	Cardiotocography
ECG	Electrocardiography
Exp #	Experiment number
fECG	Fetal electrocardiography
FBS/FSBS	Fetal scalp blood sampling
F0	Frontal scalp lead
GA	Gestational age
HIE	Hypoxic ischemic encephalopathy
IQR	Interquartile range
LR -	Negative likelihood ratio
LR+	Positive likelihood ratio
MMC	Máxima Medical Center
n	Number
NICU	Neonatal Intensive Care Unit
O0	Occipital scalp lead
OR	Diagnostic odds ratio
pHart	pH of the arterial umbilical cord blood
RCT	Randomized controlled trial
ROC	Receiver operator characteristic
RSTAN	Relative ST analysis
SA node	Sinoatrial node
SD	Standard deviation
STAN	ST analysis
T/QRS ratio	The quotient between T-amplitude and QRS-amplitude
UMCU	University Medical Center Utrecht
VCG	Vectorcardiogram
WCT	Wilson Central Terminal

List of publications

Journal papers

Verdurmen, K. M. J., **Hulsenboom, A. D. J.**, van Laar, J. O. E. H., Wijn, P. F. F., Vullings, R., & Oei, S. G. (2016). Orientation of the electrical heart axis in mid-term pregnancy. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, *207*. https://doi.org/10.1016/j.ejogrb.2016.10.030

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Curriculum Vitae

Olenka Hulsenboom werd geboren op 25 november 1989 in Tilburg, Nederland, en groeide in diezelfde stad op in een Nederlands-Pools gezin. In 2008 behaalde zij cum laude haar gymnasiumdiploma aan het Theresialyceum te Tilburg, waarna zij startte met haar studie Geneeskunde aan Maastricht University. Zij studeerde af in 2014 na haar oudste coschap en wetenschappelijke stage op de afdeling obstetrie/gynaecologie van het Máxima Medisch Centrum te Veldhoven onder supervisie van prof. dr. S. G. Oei (MMC, Veldhoven) en dr. ir. R. Vullings (Eindhoven University of Technology, Eindhoven).

In september 2014 zette zij haar onderzoek voort naar het foetaal elektrocardiogram als arts-onderzoeker van de onderzoeksgroep Fundamentele Perinatologie. De resultaten hiervan worden gepresteerd in dit proefschrift. Zij volgde de post-master opleiding seksuologie aan de RINO-groep te Utrecht en werkte in 2017 als arts-assistent niet in opleiding tot specialist obstetrie/gynaecologie in het MMC.

In 2018 koos zij voor een andere richting en volgde zij de huisartsopleiding aan het Radboud UMC te Nijmegen tot 2021. Sindsdien werkt zij als waarnemend huisarts.

Olenka woont met haar man Joris in Tilburg. In augustus 2022 is hun dochter Janna geboren.