Fetal autonomic cardiac response during pregnancy and labour

Fetal autonomic cardiac response during pregnancy and labour

Judith van Laar

Cover design by Angelique Lemmens
Photograph by Angelique Lemmens
Lay-out by Henk Dinnissen
Printed by Ipskamp drukkers

Financial support for the publication of this thesis has been kindly provided by Philips Healthcare (main sponsor of printing), Stichting de Weijerhorst, Merck Sharp & Dohme B.V., ChipSoft B.V., Nemo Healthcare, GrafiMedics B.V., Monica Healthcare Ltd, BMA B.V. (Mosos), Medical Dynamics, Unitron Group B.V., Ferring Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Mortara Instrument B.V. and Memidis Pharma B.V.

A catalogue record is available from the Eindhoven University of Technology Library
ISBN 978-90-386-3176-9
NUR 954

Fetal autonomic cardiac response during pregnancy and labour

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Technische Universiteit Eindhoven, op gezag van de rector magnificus, prof.dr.ir. C.J. van Duijn, voor een commissie aangewezen door het College voor Promoties in het openbaar te verdedigen op woensdag 31 oktober 2012 om 16.00 uur

door

Judith Octavie Elisabeth Helena van Laar

geboren te Sittard

Dit proefschrift is goedgekeurd door de promotoren:

prof.dr. S.G. Oei
en
prof.dr.ir. P.F.F. Wijn

Copromotor:
dr.ir. R. Vullings

Samenstelling van de promotiecommissie:

prof.dr. S.G. Oei, promotor
Technische Universiteit Eindhoven

prof.dr.ir. P.F.F. Wijn, promotor
Technische Universiteit Eindhoven

dr.ir. R. Vullings, copromotor
Technische Universiteit Eindhoven

prof.dr.ir. J.W.M. Bergmans, lid TU/e
Technische Universiteit Eindhoven

prof.dr. J.G. Nijhuis, extern lid
Maastricht Universitair Medisch Centrum

prof.dr. F.P.H.A. Vandenbussche, extern lid
Universitair Medisch Centrum St Radboud, Nijmegen

prof.dr. G.H.A. Visser, extern lid
Universitair Medisch Centrum Utrecht

prof.dr.ir. A.C.P.M. Backx, voorzitter
Technische Universiteit Eindhoven

Contents

Chapter 1	General introduction and outline of the thesis	9
Chapter 2	Physiological background	21
Chapter 3	Technical background	35
Chapter 4	Spectral analysis of fetal heart rate variability for fetal surveillance: review of the literature *(Acta Obstet Gynecol Scand 2008;87:300-306)*	43
Chapter 5	Fetal autonomic response to severe acidaemia during labour *(BJOG 2010;117:429-437)*	57
Chapter 6	Normalized spectral power of fetal heart rate variability is associated with fetal scalp blood pH *(Early Hum Dev 2011;87:259-263)*	73
Chapter 7	Power spectrum analysis of fetal heart rate variability at near term and post term gestation during active sleep and quiet sleep *(Early Hum Dev 2009;85:795-798)*	87
Chapter 8	Beat-to-beat heart rate detection in multi-lead abdominal fetal ECG recordings *(Med Eng Phys 2012;34:333-338)*	99
Chapter 9	Fetal heart rate variability in frequency-domain during pregnancy, obtained from non-invasive electrocardiogram recordings *(Submitted)*	115
Chapter 10	Summary and general discussion	133
Addendum	Nederlandse samenvatting	148
	List of abbreviations	153
	List of publications	154
	Dankwoord	156
	Curriculum vitae	159

Chapter 1

General introduction and outline of the thesis

General introduction

The task of an obstetrician is a safe pregnancy and delivery for mother and child. Although most pregnancies and deliveries are uncomplicated, antenatal and perinatal mortality rates in the Netherlands remain relatively high and are of concern to obstetricians and politicians[1]. To reduce the occurrence of fetal complications during pregnancy and labour, timely and valid recognition of fetal distress is needed to intervene promptly and appropriately. By doing so, fetal metabolic acidosis, which is associated with severe perinatal morbidity and mortality[2,3], can be reduced. In addition, unnecessary medical interventions, which are associated with increased neonatal and maternal morbidity and mortality, can also be abated. This is of great importance during the preterm period, since unnecessary interventions in premature fetuses result in iatrogenic preterm births, while preterm birth is the most frequent cause of infant death[4]. However, the timing of medical intervention is extremely difficult since the current methods of fetal monitoring have limited diagnostic value in detecting fetal distress. Therefore, improved monitoring of fetal condition during pregnancy and labour is of major importance.

Present day fetal surveillance

Fetal monitoring aims to identify the fetus at risk for long term injury resulting from asphyxia. Throughout pregnancy and during labour the fetal condition can be assessed by a variety of tests.

Fetal surveillance during labour

Fetal heart sounds have been obtained by listening with the Pinard's stethoscope for over 100 years. Continuous electronic fetal heart rate monitoring was introduced during the 1960s. Cardiotocography, the simultaneous registration of fetal heart rate and uterine activity has become the worldwide standard method of fetal monitoring during labour, although it appeared to have limited diagnostic value[5]. An example of a cardiotocogram (CTG) registration is given in Figure 1.1. Although CTG has a high sensitivity, the poor specificity of this method resulted in increased rates of operative vaginal delivery and caesarean section[5]. CTG was associated with halving of neonatal seizures, but no differences in cerebral palsy or other measures of fetal wellbeing were seen[5]. Possible long term effects of this decrease in neonatal seizures are not yet fully assessed as long term neurological follow up is missing. Thus, CTG might be a useful screening test for fetal monitoring; it nevertheless requires additional diagnostic tests in case of suspected fetal compromise to avoid unnecessary operative deliveries.

Fetal scalp blood sampling (FBS) during labour, in case of an abnormal CTG, is reported to be useful for reducing unnecessary interventions[6]. However, the evidence for this is weak[7]. Contrary to current practice recommendations, no evidence is found that the increase in caesarean section rate, due to CTG monitoring, is greater when FBS is unavailable; nor does FBS influence the fetal outcome[5]. Some authors claim that FBS can be virtually eliminated without an increase in caesarean section rate[8]. Obtaining a blood

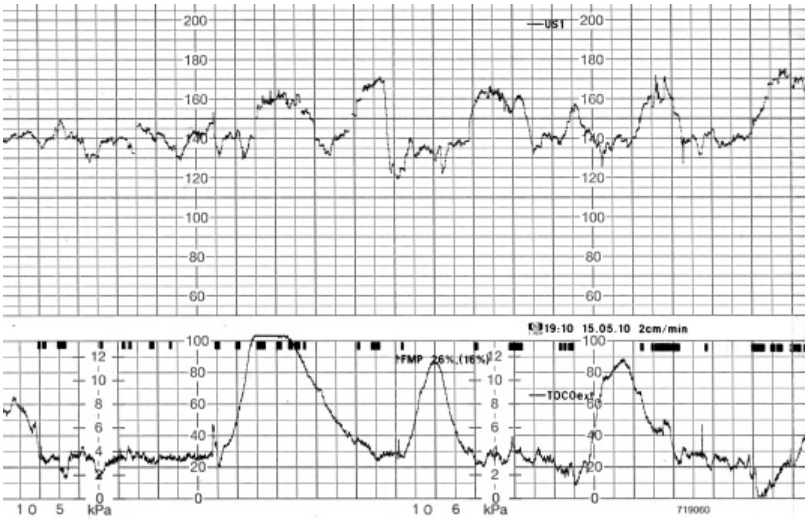


Figure 1.1. Example of a cardiotocogram. Upper line: fetal heart rate. Lower line: uterine contractions.

sample requires rupture of the fetal membranes and cervical dilatation. A disadvantage of FBS is that a sample can be contaminated with maternal blood or amniotic fluid and that contact between blood and air causes a lowering of CO_2 which results in an increase in pH. Other limitations to the information obtained by FBS are that it only provides instantaneous information and that the sample is obtained from blood which originates from peripheral tissue. Normal labour hypoxia (during contractions) causes a redistribution of blood flow from peripheral to central organs. Due to this reduction in peripheral blood flow, local accumulation of CO_2 can occur and respiratory acidaemia takes place in peripheral tissue while only in an advanced stage the central organs may be affected. On the other hand, metabolic acidosis develops in the tissues and time is required for the free hydrogen ions to be transported from the tissues into the blood. In early stage metabolic acidosis a scalp pH can be within the normal range. Despite these disadvantages, FBS is reported to be a valid technique for determining fetal acid-base status during labour[9], since a good correlation exists between scalp blood pH taken shortly before delivery and newborn umbilical cord pH[10]. Unfortunately, FBS is not free of risks, it has a reported overall incidence of complications of 6%, of which haemorrhage and infections are the major problems[6]. While some authors question the value of intrapartum FBS[7], since there is no high quality evidence that FBS influences the caesarean section rate or fetal outcome[5,7], others suggest that FBS is not used adequately in clinical practice[11].

In recent years, automatic ST-waveform analysis of the fetal electrocardiogram (ECG; STAN®, Neoventa Medical, Moelndal, Sweden) was developed to provide continuous additional information on the fetal condition. The STAN® concept is based on the ability of the ST-segment to reflect fetal distress[12,13]. The changes in fetal ECG, reported to

be associated with fetal distress are either an increase in T-wave, quantified by the ratio between the T-wave amplitude and the QRS amplitude (T/QRS), or a biphasic ST-pattern[14]. An increase in the T-wave is due to the hypoxia-induced adrenalin surge which activates β-receptors which, in turn, results in the release of glycogen[12,13]. With this release in glycogen, potassium ions are set free and, as a result, the amplitude of the T-wave increases[12,13,15]. Due to glycogenolysis, lactate is produced and this contributes to the development of metabolic acidosis. A biphasic ST-segment is related to myocardial hypoxia whereby the fetus had no time to respond or to reduced capacity of the fetal heart to respond due to lacking resources[13].
STAN® in addition to CTG monitoring is nowadays applied for fetal monitoring. At first it was reported that combined use of CTG and STAN® during labour at term reduced the rate of severe metabolic acidosis at birth and operative delivery for fetal distress[16]. Recent meta-analyses confirmed that CTG and STAN® resulted in less operative vaginal deliveries, when compared to CTG alone[17,18]. However, although there was a non-significant trend in decreased rates of metabolic acidosis at birth, there was no significant difference in fetal outcome or caesarean delivery rate[17,18]. STAN® decreased the need for FBS[17,18] but cannot be used adequately without the availability of FBS analysis[19,20]. This is due to the limited reliability of STAN® in clinical practice under certain conditions. For instance, STAN® is not reliable in case of an abnormal CTG at start of a registration, during periods of poor signal quality, and during prolonged periods of an abnormal CTG pattern without ST-events[20,21].

Recently, fetal pulse oximetry was introduced as an adjunct to CTG. This technology was designed to improve knowledge of the fetal condition by continuously measuring fetal oxygen saturation in the presence of a non-reassuring fetal heart rate pattern. With fetal pulse oximetry, a sensor is inserted through the cervix after the membranes have ruptured and is positioned against the fetal face. Once in contact with the fetal skin, the device permits measurement of fetal oxygen saturation during labour. It was thought that the knowledge of fetal oxygen saturation would improve diagnostic value. However, pulse oximetry was neither associated with a reduction in the rate of operative delivery nor with an improvement in the condition of the newborn[22,23]. It was suggested that this might be due to the frequently observed low oxygen saturation in case of a normal fetal condition[22]. Others suggested that the overall caesarean section rate did not drop due to an increase in caesarean section rate for dystocia, because a non-reassuring CTG may indicate an underlying risk for dystocia[23]. In other words, a decrease in caesarean section rate for presumed fetal distress will eventually result in an increase in caesarean section rate for dystocia.

The above mentioned diagnostic techniques, used in addition to CTG, have limited value to detect fetal distress and they can only be applied during labour at term, after rupture of the membranes and sufficient dilatation of the cervix. Furthermore, they remain dependent on the subjective assessment of CTG registration, which has a high inter- and intraobserver variability rate[24].

Fetal surveillance during pregnancy

Throughout pregnancy, the fetal condition can be assessed with tests, mainly based on ultrasound technology. Although external CTG registration during pregnancy is widely adopted, it is known to have important limitations[25,26]. The fetal heart rate is detected from an ultrasound sensor located on the maternal abdomen. This external recorder has limited reliability to obtain accurate fetal heart rate recordings. External CTG registration results in over 10 percent of erroneous accelerations and decelerations. These errors are caused by the fetal heart rate monitor and may contribute to the high inter- and intraobserver variation in visual analysis[26]. Furthermore, external CTG produces an averaged fetal heart rate and therefore cannot give beat-to-beat heart rate variability[25]. There is no evidence that antenatal CTG registration improves perinatal outcome[27]. Despite the limited validity and reliability of this method as a test of fetal assessment, it has widely infiltrated maternity care practice.
In addition to the external CTG technology a biophysical profile can be obtained. This profile combines ultrasonic monitoring of fetal movements, fetal tone and fetal breathing, with the assessment of amniotic fluid and fetal heart rate. The biophysical profile is performed in an effort to identify babies that may be at risk for poor pregnancy outcome, so that additional assessment of wellbeing or an intervention to expedite birth may be performed. However, biophysical profile assessment compared to conventional CTG resulted in an increase in caesarean section rate without improving perinatal outcome[28]. Therefore at present, insufficient evidence exists to support the use of the biophysical profile as a test of fetal wellbeing.

Future prospects of fetal surveillance

There is an urgent need to develop methods that provide complementary information on fetal wellbeing to enable appropriate intervention. Complementary information should be obtained non-invasively to enable intra- and antepartum use during the term and preterm period. This is extremely important for premature fetuses. Firstly, CTG is often indecisive in premature fetuses (also antepartum) and unnecessary intervention results in iatrogenic preterm birth, while preterm birth is the most frequent cause of infant morbidity and mortality[4]. Secondly, an adverse acid-base status at birth is additive to the effect of gestational age concerning the risk of neurologic impairment after preterm birth[29]. Thirdly, asphyxia is more frequent after preterm birth and is often already present antepartum in premature fetuses[30], resulting in a further increased risk of long term morbidity and mortality after preterm birth. Therefore, non-invasive additional information on fetal condition is needed.

Currently, studies focus on the use of computerised CTG analysis[31]. Computerised CTG analysis systems were developed with the aim of bringing validity and reliability to CTG interpretation. It was also thought that the computerised CTG analysis might be able to extract more diagnostic information from the fetal heart rate signal than visual analysis alone. Well-known is the Sonicaid system (Huntleigh, Cardiff, UK) based on the work of Redman and Dawes[32]. The short term variation (STV) was shown to be the

most prognostic parameter in antepartum fetal heart rate recordings. Decreased STV was associated with fetal acidaemia[33,34]. Although computerised CTG analysis gives an objective assessment, it did not perform better than visual assessment by experienced obstetricians[35].
Recently, the Omniview-SisPorto® system (Speculum, Lisbon, Portugal) was developed[36]. It provides automated analysis of CTG that closely follows the FIGO guidelines[37]. The system's CTG analysis is in good agreement with the visual assessment by experts[38] and the program's alerts are predictive of fetuses born with severe acidaemia[39]. It seems that automated assessment of the heart rate parameters may overcome some of the weaknesses associated with human interpretation of the CTG, such as low reproducibility due to inter- and intraobserver variation in interpretation. However, although preliminary findings appear encouraging, it is necessary to determine whether the use of computerised CTG analysis will reduce intervention rate and improve perinatal outcome. Currently, a multicenter clinical trial is carried out to determine the diagnostic value of intrapartum computerised CTG analysis[31].

The (computerised) fetal heart rate variability (HRV) assessment in the time-domain lacks a physiological background. More knowledge exists on physiological interpretation of HRV measures in the frequency-domain[40]. Additional information on fetal wellbeing might be obtained by assessment of fetal HRV in the frequency-domain. The normal heart rate fluctuates under the influence of the centrally mediated changes in sympathetic and parasympathetic tone[41]. Therefore, quantifying the variations in heart rate by spectral analysis can be used to monitor autonomic nervous system activity and may provide an early diagnostic tool for detecting fetal distress[42,43].

Spectral analysis can be performed on beat-to-beat heart rate calculated from fetal ECG recordings[44]. It determines the energy in specific frequency components of HRV. In human adults the low frequency (LF) cardiovascular fluctuations are ascribed to the baroreceptor reflex and are under sympathetic and parasympathetic control[40]. The high frequency (HF) fluctuations are associated with respiration and are under parasympathetic control only[40]. The ratio of the LF and HF powers (LF/HF) was reported to provide a marker of the sympathovagal balance in the control of heart rate[40]. In human adults it is confirmed that autonomic nervous system modulation is a strong and independent predictor of morbidity and mortality in diabetic and myocardial disease[40].

Frequency-domain analysis contributes to the understanding of autonomic modulation of fluctuations in heart rate. Very little is known about the use of spectral analysis of fetal HRV to evaluate the fetal autonomic nervous system modulation. Since spectral analysis of fetal HRV might improve our understanding of the physiological response of the human fetus to distress, it might create valuable insight into pathophysiological conditions. Because the current methods of fetal monitoring have poor diagnostic value, increased knowledge about the fetal cardiovascular response to stress might improve fetal monitoring.

Outline of the thesis

This thesis concerns the fetal autonomic cardiac response during pregnancy and labour. Physiological and technical background information is provided in chapter 2 and 3. Autonomic cardiac control is reflected in LF and HF spectral power of beat-to-beat HRV. An overview of the available literature on spectral analysis of fetal HRV for fetal monitoring is provided in chapter 4. In chapter 5, the fetal autonomic cardiac response to severe fetal distress during labour at term is presented and compared with normal fetal condition. In chapter 6, a study is presented in which the association between LF and HF spectral power of fetal HRV and fetal scalp blood pH is examined. In this chapter it is studied whether spectral estimates of fetal HRV can be used to detect fetal distress in an early stage. The effect of fetal behavioural state on spectral estimates during labour around term is shown in chapter 7. In this chapter it is also examined whether spectral estimates are influenced by gestational age. Hence, it is determined whether behavioural state and gestational age should be taken into consideration, before using spectral analysis of fetal HRV for fetal monitoring around term. In chapters 5 to 7, spectral analysis is performed on fetal beat-to-beat heart rate derived from direct fetal ECG measurement, obtained by fetal scalp electrode. This measurement can only be performed during labour after rupture of the membranes and sufficient dilatation. Chapters 8 and 9 use beat-to-beat fetal heart rate derived non-invasively from indirect fetal ECG measurement, obtained from skin electrodes on the maternal abdomen. Chapter 8 describes and evaluates the performance of an algorithm that is developed to obtain fetal beat-to-beat heart rate from fetal ECG recordings with poor signal-to-noise ratio. In chapter 9, spectral estimates of fetal HRV are determined longitudinally during uncomplicated pregnancy to study fetal autonomic cardiac development. Finally, a summary and general discussion is provided and future perspectives are discussed in chapter 10.

Chapters 4 to 9 have either been published or submitted for publication. Therefore, each chapter is written to be self-contained, causing some overlap in the introduction and methods sections of the chapters.

Goals of the thesis

1. To study fetal autonomic cardiac response in case of severe fetal distress.

2. To determine whether spectral estimates of fetal HRV are associated with fetal scalp blood pH.

3. To study whether spectral estimates of fetal HRV are related to gestational age. To determine whether gestational age should be corrected for, before using spectral analysis for fetal monitoring.

4. To study whether spectral estimates of fetal HRV are associated with fetal behavioural state. To determine whether behavioural states should be accounted for while using spectral analysis for fetal monitoring.

5. To evaluate an algorithm for retrieving fetal ECG and fetal beat-to-beat heart rate from non-invasive recordings and assess whether these non-invasive heart rate data, can be used for antepartum spectral analysis.

6. To evaluate changes in spectral estimates of fetal HRV as a function of gestational age from longitudinal measurements. To examine the development of the fetal autonomic nervous system during pregnancy.

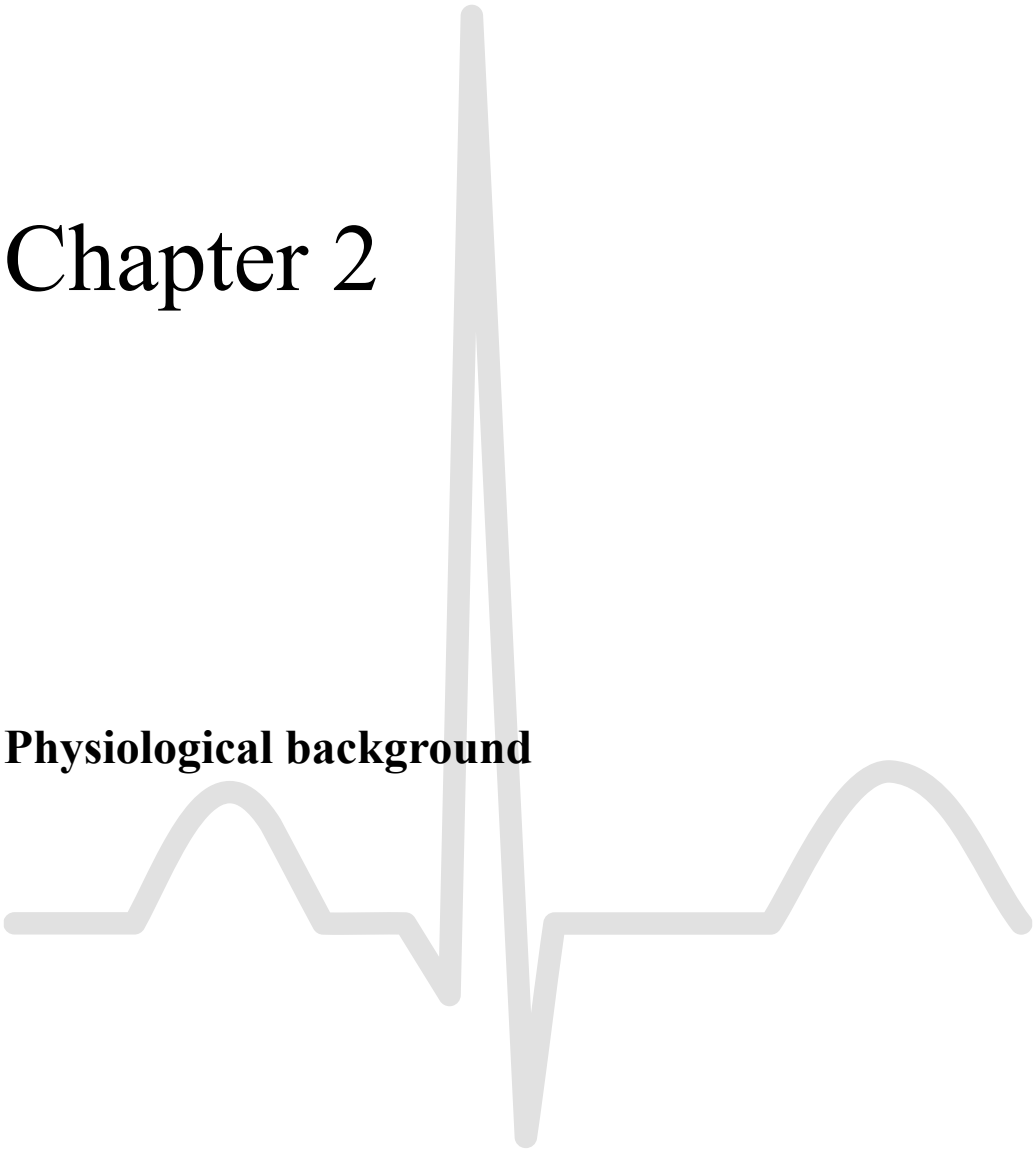
References

1. Mohangoo AD, Buitendijk SE, Hukkelhoven CW, Ravelli AC, Rijninks-van Driel GC, Tamminga P, Nijhuis JG. Higher perinatal mortality in The Netherlands than in other European countries: the Peristat-II study. Ned Tijdschr Geneeskd 2008;152:2718-2727.
2. Victory R, Penava D, Da Silva O, Natale R, Richardson B. Umbilical cord pH and base excess values in relation to adverse outcome events for infants delivering at term. Am J Obstet Gynecol 2004;191:2021-2028.
3. Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. Am J Obstet Gynecol 1997;177:1391-1394.
4. Callaghan WM, MacDorman MF, Rasmussen SA, Qin C, Lackritz EM. The contribution of preterm birth to infant mortality rates in the United States. Pediatrics 2006;118:1566-1573.
5. Alfirevic Z, Devane D, Gyte GML. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. Cochrane Database Syst Rev 2008.
6. Young DC, Gray JH, Luther ER, Peddle LJ. Fetal scalp blood pH sampling: its value in an active obstetric unit. Am J Obstet Gynecol 1980;136:276-281.
7. Mahendru AA, Lees CC. Is intrapartum fetal blood sampling a gold standard diagnostic tool for fetal distress? Eur J Obstet Gynecol Reprod Biol 2011;156:137-139.
8. Goodwin TM, Milner-Masterson L, Paul RH. Elimination of fetal scalp blood sampling on a large clinical service. Obstet Gynecol 1994;83:971-974.
9. Parer JT. The current role of intrapartum fetal blood sampling. Clin Obstet Gynecol 1980;23: 565-582.
10. Yoshioka T, Roux JF. Correlation of fetal scalp blood pH, glucose, lactate and pyruvate concentrations with cord blood determinations at time of delivery and cesarean section. J Reprod Med 1970;5: 209-214.
11. Westgate J, Greene K. How well is fetal blood sampling used in clinical practice? Br J Obstet Gynaecol 1994;101:250-251.
12. Rosen KG, Dagbjartsson A, Henriksson BA, Lagercrantz H, Kjellmer I. The relationship between circulating catecholamines and ST waveform in the fetal lamb electrocardiogram during hypoxia. Am J Obstet Gynecol 1984;149:190-195.
13. Westgate JA, Bennet L, Brabyn C, Williams CE, Gunn AJ. ST waveform changes during repeated umbilical cord occlusions in near-term fetal sheep. Am J Obstet Gynecol 2001;184:743-751.
14. Sundstrom AK, Rosen D, Rosen KG. Fetal surveillance. Neoventa Medical, Goteborg, Sweden 2000. Page 1-38.
15. Hökegård KH, Karlsson K, Kjellmer I, Rosen KG. ECG-changes in the fetal lamb during asphyxia in relation to beta-adrenoceptor stimulation and blockade. Acta Physiol Scand 1979;105:195-203.
16. Amer-Wåhlin I, Hellsten C, Norén H, Hagberg H, Herbst A, Kjellmer I, Lilja H, Lindoff C, Månsson M, Mårtensson L, Olofsson P, Sundström A, Marsál K. Cardiotocography only versus cardiotocography plus ST analysis of fetal electrocardiogram for intrapartum fetal monitoring: a Swedish randomised controlled trial. Lancet 2001;358:534-538.
17. Neilson JP. Fetal electrocardiogram (ECG) for fetal monitoring during labour. Cochrane Database Syst Rev 2012.
18. Becker JH, Bax L, Amer-Wåhlin I, Ojala K, Vayssière C, Westerhuis ME, Mol BW, Visser GH, Maršál K, Kwee A, Moons KG. ST analysis of the fetal electrocardiogram in intrapartum fetal monitoring: a meta-analysis. Obstet Gynecol 2012;119:145-154.

19. Amer-Wahlin I, Arulkumaran S, Hagberg H, Marsal K, Visser GH. Fetal electrocardiogram: ST waveform analysis in intrapartum surveillance. BJOG 2007;114:1191-1193.
20. Becker JH, Westerhuis ME, Sterrenburg K, van den Akker ES, van Beek E, Bolte AC, van Dessel TJ, Drogtrop AP, van Geijn HP, Graziosi GC, van Lith JM, Mol BW, Moons KG, Nijhuis JG, Oei SG, Oosterbaan HP, Porath MM, Rijnders RJ, Schuitemaker NW, Wijnberger LD, Willekes C, Visser GH, Kwee A. Fetal blood sampling in addition to intrapartum ST-analysis of the fetal electrocardiogram: evaluation of the recommendations in the Dutch STAN® trial. BJOG 2011;118:1239-1246.
21. Westerhuis ME, Kwee A, van Ginkel AA, Drogtrop AP, Gyselaers WJ, Visser GH. Limitations of ST analysis in clinical practice: three cases of intrapartum metabolic acidosis. BJOG 2007;114: 1194-1201.
22. Bloom SL, Spong CY, Thom E, Varner MW, Rouse DJ, Weininger S, Ramin SM, Caritis SN, Peaceman A, Sorokin Y, Sciscione A, Carpenter M, Mercer B, Thorp J, Malone F, Harper M, Iams J, Anderson G. Fetal pulse oximetry and cesarean delivery. N Engl J Med 2006;355:2195-2202.
23. East CE, Begg L, Colditz PB. Fetal pulse oximetry for fetal assessment in labour. Cochrane Database Syst Rev 2010.
24. Nielsen PV, Stigsby B, Nickelsen C, Nim J. Intra- and inter-observer variability in the assessment of intrapartum cardiotocograms. Acta Obstet Gynecol Scand 1987;66:421-424.
25. Peters M, Crowe J, Pieri JF, Quartero H, Hayes-Gill B, James D, Stinstra J, Shakespeare S. Monitoring the fetal heart non-invasively: a review of methods. J Perinat Med 2001;29:408-416.
26. Dawes GS, Moulden M, Redman CW. Limitations of antenatal fetal heart rate monitors. Am J Obstet Gynecol 1990;162:170-173.
27. Grivell RM, Alfirevic Z, Gyte GM, Devane D. Antenatal cardiotocography for fetal assessment. Cochrane Database Syst Rev 2010.
28. Lalor JG, Fawole B, Alfirevic Z, Devane D. Biophysical profile for fetal assessment in high risk pregnancies. Cochrane Database Syst Rev 2009.
29. Gaudier FL, Goldenberg RL, Nelson KG, Peralta-Carcelen M, Johnson SE, DuBard MB, Roth TY, Hauth JC. Acid-base status at birth and subsequent neurosensory impairment in surviving 500 to 1000 gm infants. Am J Obstet Gynecol 1994;170:48-53.
30. Low JA, Killen H, Derrick EJ. Antepartum fetal asphyxia in the preterm pregnancy. Am J Obstet Gynecol 2003;188:461-465.
31. Ayres-de-Campos D, Ugwumadu A, Banfield P, Lynch P, Amin P, Horwell D, Costa A, Santos C, Bernardes J, Rosen K. A randomised clinical trial of intrapartum fetal monitoring with computer analysis and alerts versus previously available monitoring. BMC Pregnancy Childbirth 2010;10:71.
32. Dawes GS, Moulden M, Redman CW. System 8000: computerized antenatal FHR analysis. J Perinat Med 1991;19:47-51.
33. Dawes GS. The fetal ECG: accuracy of measurements. Br J Obstet Gynaecol 1993;100 Suppl 9: 15-17.
34. Street P, Dawes GS, Moulden M, Redman CW. Short-term variation in abnormal antenatal fetal heart rate records. Am J Obstet Gynecol 1991;165:515-523.
35. Cheng LC, Gibb DM, Ajayi RA, Soothill PW. A comparison between computerised (mean range) and clinical visual cardiotocographic assessment. Br J Obstet Gynaecol 1992;99:817-820.
36. Ayres-de-Campos D, Sousa P, Costa A, Bernardes J. Omniview-SisPorto 3.5 - a central fetal monitoring station with online alerts based on computerized cardiotocogram + ST event analysis. J Perinat Med 2008;36:260-264.

37. FIGO subcommittee on Standards in Perinatal Medicine. Guidelines for the use of fetal monitoring. Int J Gynaecol Obstet 1987;25:159-167.
38. Costa MA, Ayres-de-Campos D, Machado AP, Santos CC, Bernardes J. Comparison of a computer system evaluation of intrapartum cardiotocographic events and a consensus of clinicians. J Perinat Med 2010,38:191-195.
39. Costa A, Costa F, Ayres-de-Campos D, Costa F, Santos C, Bernardes J. Prediction of neonatal acidemia by computer analysis of fetal heart rate and ST event signals. Am J Obstet Gynecol 2009; 201:464. e1-6.
40. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-1065.
41. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213: 220-222.
42. Sibony O, Fouillot JP, Benaoudia M, Benhalla A, Oury JF, Sureau C, Blot P. Quantification of the fetal heart rate variability by spectral analysis of fetal well-being and fetal distress. Eur J Obstet Gynecol Reprod Biol 1994;54:103-108.
43. Chung DY, Sim YB, Park KT, Yi SH, Shin JC, Kim SP. Spectral analysis of fetal heart rate variability as a predictor of intrapartum fetal distress. Int J Gynaecol Obstet 2001;73:109-116.
44. Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Välimäki IA, Rosén KG, Ekholm EM. Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. BJOG 2005;112:418-423.

Chapter 2



Physiological background

The autonomic nervous system

The function of the autonomic nervous system is to maintain body homeostasis by coordinating responses to internal and external stimuli. The autonomic nervous system controls smooth muscle, cardiac muscle and glands. It is composed of the sympathetic and parasympathetic nervous system. The autonomic pathway includes preganglionic neurons (whose cell body is located in the central nervous system) that synapse with postganglionic neurons (whose cell body is located in one of the autonomic ganglia). The postganglionic neurons synapse with the effector organs[1].

The sympathetic preganglionic neurons are located in the cervical, thoracic and lumbar segments of the spinal cord. The parasympathetic preganglionic neurons are found in the brainstem and in the sacral spinal cord. Sympathetic postganglionic neurons are located in the pre- and paravertebral ganglia, at some distance from their effector organs. Parasympathetic postganglionic neurons are found in parasympathetic ganglia near or within the walls of their target organs[1].

The sympathetic and parasympathetic nervous system act in a coordinated way, sometimes reciprocally and sometimes synergistically to regulate visceral function[1,2]. The visceral afferent fibres supply information that originates from the sensory receptors in the viscera and form the afferent limb of the reflex arcs. The visceral reflexes operate at a subconscious level and are very important for homeostatic regulation. The neurotransmitters released by afferent fibres are not well documented[1].

The neurotransmitter at the synapses of preganglionic neurons of the sympathetic and parasympathetic ganglia is acetylcholine. The two classes of acetylcholine receptors in autonomic ganglia are nicotinic and muscarinic receptors. Both receptors mediate excitatory postsynaptic potentials, at different rates. Sympathetic postganglionic neurons generally release norepinephrine. Norepinephrine excites some effector cells and inhibits other effector cells. The receptors on the target cells are α- and β-adrenergic receptors, further subdivided into α_1, α_2, β_1, β_2. The parasympathetic postganglionic neurotransmitter is acetylcholine. Parasympathetic postganglionic actions are mediated by muscarinic receptors, further subdivided into M_1 and M_2. Muscarinic receptors like adrenergic receptors have diverse actions[1].

The endocrine cells of the adrenal medulla are similar to the sympathetic postganglionic neurons. They receive input from the preganglionic neurons, are excited by acetylcholine and release catecholamines. However, the adrenal medulla cells differ from sympathetic postganglionic neurons in that they release catecholamines into the circulation rather than synaptically[1].

A simplified schematic overview of the autonomic nervous system is given in Figure 2.1.

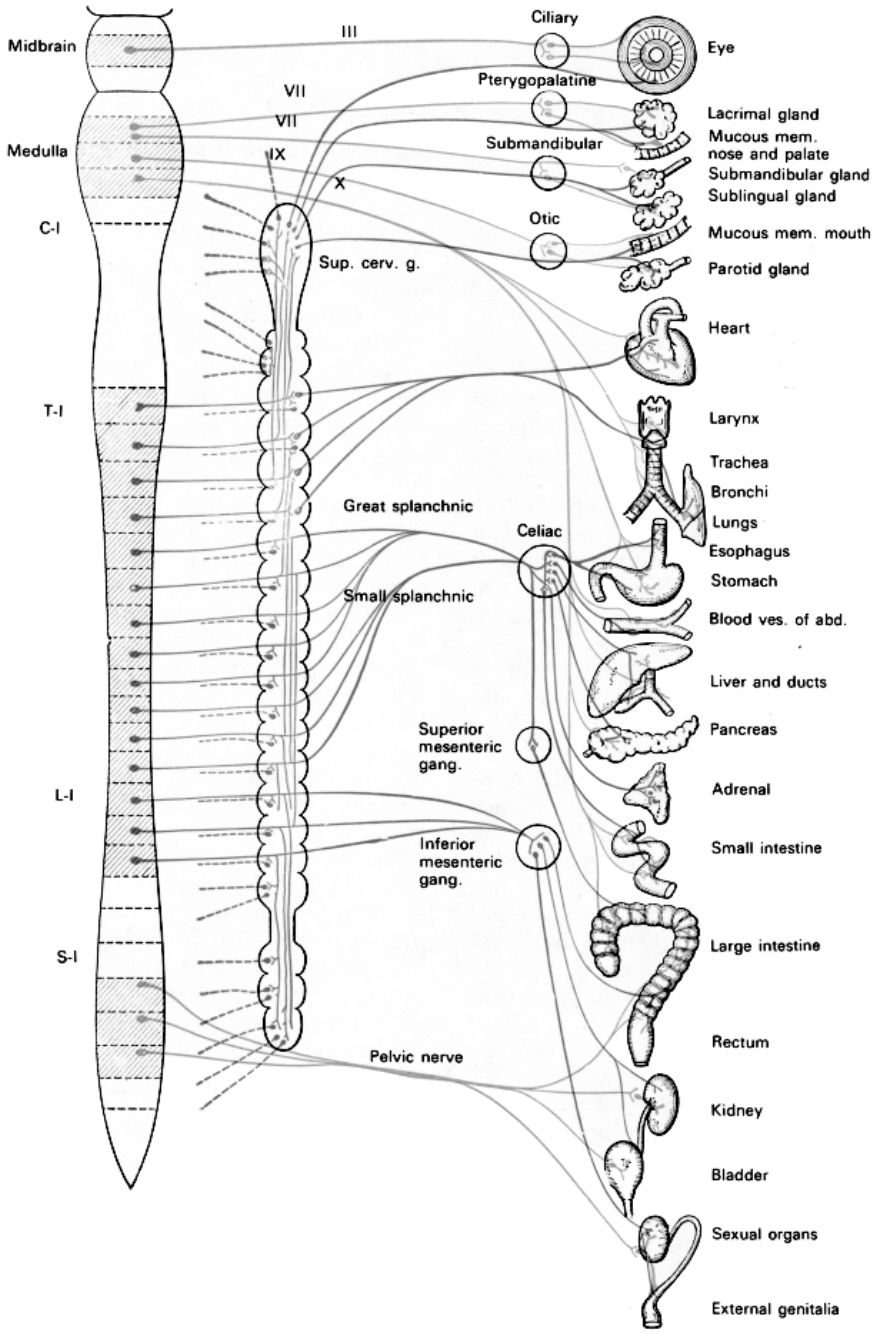


Figure 2.1. The autonomic nervous system. The sympathetic nervous system is shown in red. The parasympathetic nervous system is shown in blue. From Gray's Anatomy of the Human Body.

Autonomic cardiac control

For this thesis we are interested in the autonomic control of heart rate. The autonomic nervous system is the principal means by which heart rate is controlled. Both divisions of the autonomic nervous system influence the sinoatrial (SA) node of the heart. The sympathetic system enhances the cardiac pace maker, whereas the parasympathetic system inhibits it. Changes in heart rate usually involve a reciprocal action of these two divisions of the autonomic nervous system. The heart rate increases with a decrease in parasympathetic activity or an increase in sympathetic activity. The heart rate decreases with the opposite activity. Parasympathetic tone usually predominates in healthy, resting mature individuals[3].

The cardiac parasympathetic fibres originate in the medulla oblongata. In humans, the vagal fibres pass through the neck close to the common carotid arteries and then through the mediastinum to synapse with the postganglionic cells. The postganglionic cells are located either on the epicardial surface or within the walls of the heart. Most of the cardiac ganglion cells are located near the SA node and the atrioventricular (AV) conduction tissue. The right vagus nerve mainly affects the SA node. Stimulation slows SA nodal firing. The left vagus nerve mainly inhibits AV conduction tissue to produce various degrees of AV block[3].

The SA and AV nodes are rich in cholinesterase, an enzyme that breaks down acetylcholine. Therefore, the effect of vagal stimulation decays very quickly when vagal stimulation is discontinued. Because acetylcholine activates special acetylcholine regulated K^+ channels in the cardiac cells (without the need for a second messenger system), the effect of vagal stimulation is very fast. The brief latency and the rapid decay of the vagal response permit the parasympathetic system to exert a beat-to-beat control of SA and AV nodal function. In human adults, parasympathetic influences usually dominate sympathetic effects at the SA node[3].

The cardiac sympathetic fibres originate in the upper thoracic and lower cervical segments of the spinal cord. The pre- and postganglionic neurons synapse in the stellate ganglia. The postganglionic sympathetic and the preganglionic parasympathetic fibres join in the mediastinum to form a plexus of mixed efferent nerves to the heart. The postganglionic sympathetic fibres approach the base of the heart along the adventitial surface of the great vessels. These fibres are distributed to the various chambers of the heart and penetrate the myocardium, accompanying the coronary vessels. The left and right sympathetic fibres are distributed to different areas of the heart. The fibres on the left side mainly increase myocardial contractility, whereas the fibres on the right side mainly increase heart rate[3].

Unlike the vagal response, the effect of sympathetic stimulation decays relatively slowly after discontinuation of stimulation. Most of the norepinephrine released during sympathetic activation is taken up in the nerve terminals and the remainder is carried away by the blood stream. These processes are relatively slow. In addition, the sympathetic

stimulatory effect on the heart occurs more slowly than the inhibitory effect of vagal stimulation. This is due to the relatively slow norepinephrine release from the cardiac sympathetic nerve terminals. Furthermore, the effect of norepinephrine on the heart is mainly mediated via a relatively slow second messenger system. Hence, the sympathetic influence on heart rate and AV conduction is slower than the vagal influence. This implies that, the rapid cardiac vagal response allows for beat-to-beat parasympathetic modulation of heart rate, whereas the slow response to sympathetic modulation cannot exert this[3]. Therefore it is assumed that the faster fluctuations in heart rate are associated with the parasympathetic system, whereas slower fluctuations are related to sympathetic and parasympathetic modulation[2,4].

Autonomic cardiac reflex mechanisms

To understand how various physiological processes induce changes in heart rate, the autonomic cardiac reflex mechanisms have to be known. The autonomic reflex mechanisms that are mainly responsible for fluctuations in heart rate in human adults, are discussed briefly in the next paragraphs. The linkage between autonomic cardiac modulation and spectral analysis of fetal heart rate variability is discussed in chapter 3. Because humoral influences and thermoregulation induce long term regulation (very low frequent fluctuation) of heart rate[5,6], the influence of these factors on heart rate are beyond the scope of this thesis and are therefore not further discussed in this chapter.

Baroreceptor reflex

The baroreceptors are located in the aortic arch and carotid sinuses. When a sudden change in arterial blood pressure is sensed by the baroreceptors, a reflex is initiated that leads to an inverse change in heart rate. When arterial blood pressure decreases, heart rate increases due to increased sympathetic and decreased vagal activity. Conversely, when arterial blood pressure increases, the heart rate decreases due to increased vagal activity and decreased sympathetic activity[3]. A simplified schematic overview of the baroreceptor reflex loop is given in Figure 2.2.

Bainbridge reflex

Both atria have receptors that are affected by changes in blood volume. Distension of these atrial receptors results in efferent impulses from the sympathetic and the parasympathetic system to the SA node. The cardiac response to these changes in autonomic activity is highly selective. An increase in right atrial pressure stimulates atrial receptors that evoke a neurally induced increase in heart rate by the Bainbridge reflex[3].

Respiratory sinus arrhythmia

Rhythmic variations in heart rate, occurring at the frequency of respiration, appear in most individuals. The heart rate accelerates during inspiration and decelerates during expiration. Sympathetic activity increases during inspiration while parasympathetic activity increases during expiration. Because the parasympathetic cardiac response is

very quick it permits the heart rate to vary rhythmically at the respiratory frequency. Because the sympathetic system is relatively slow, the rhythmic variation in sympathetic activity does not induce oscillatory changes in heart rate. Therefore, respiratory sinus arrhythmia (RSA) is accomplished by changes in vagal activity. RSA is exaggerated when vagal tone is enhanced[3].
Stretch receptors in the lung, stimulated during inspiration, lead to a reflex increase in heart rate. The afferent and efferent limbs of this reflex are located in the vagus nerve. In addition, intrathoracic pressure decreases during inspiration which increases venous return to the right side of the heart. This results in a stretch of the right atrium which increases heart rate by the Bainbridge reflex. The increased cardiac output raises arterial blood pressure. This rise in blood pressure in turn reduces heart rate through the baroreceptor reflex[3]. Central factors are also responsible for respiratory cardiac arrhythmia. The respiratory centre in the medulla also directly influences the cardiac autonomic centres[3].

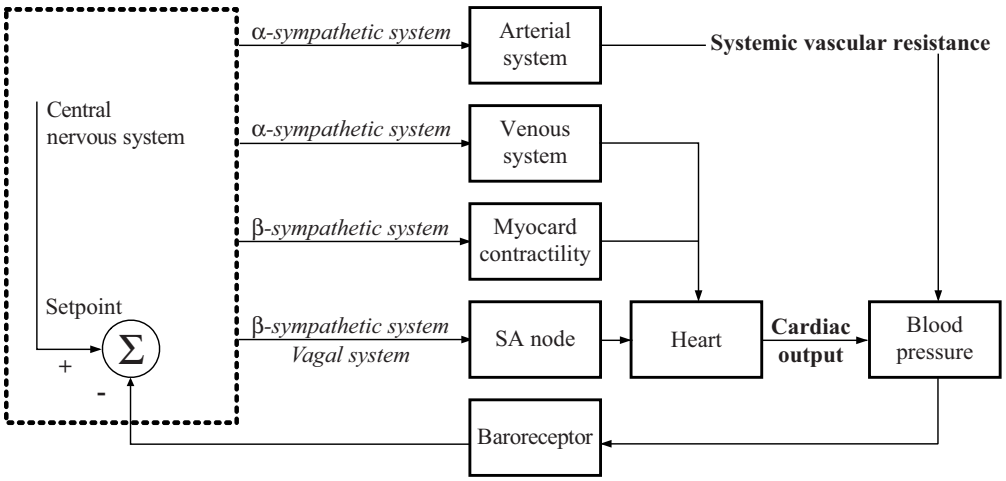


Figure 2.2. Schematic overview of the baroreceptor reflex loop.

Chemoreceptor reflex

The cardiac response to chemoreceptor stimulation is the result of primary and secondary reflex mechanisms. The primary effect of chemoreceptor stimulation is to excite the cardiac vagal centre and to decrease heart rate. Secondary effects are mediated by the respiratory system. Respiratory stimulation by arterial chemoreceptors inhibits the medullary vagal centre by inducing hypocapnia and increased lung stretch. This results in an increase in heart rate. When the pulmonary response to chemoreceptor stimulation is blocked, the heart rate response may be exaggerated[3].

Ventricular receptor reflex

Sensory receptors located in the ventricular walls are excited by various mechanical and chemical stimuli. Excitation of these ventricular receptors diminishes heart rate and peripheral resistance mediated by an increase in vagal and a decrease in sympathetic

neural activity. An example of a ventricular receptor reflex is the Bezold-Jarisch reflex, a vagally mediated depressor reflex characterised by bradycardia, hypotension and withdrawal of efferent sympathetic activity[3].

Fetal autonomic cardiac reflex mechanisms

Although there is a large body of knowledge regarding the adult autonomic cardiac system, understanding of the maturation of autonomic reflexes in human fetal life is limited. The fetal reflex responses partly differ from the adult responses due to a possibly immature autonomic nervous system, the presence of circulatory shunts (foramen ovale, ductus arteriosus and ductus venosus), the presence of the placental vascular bed and the absence of respiration.
The occurrence of RSA is well-established during periods with breathing movements in human fetuses at term[7,8]. However, RSA was not observed during breathing movements in preterm fetuses[9]. In addition, the baroreceptor reflex is already present during the second half of pregnancy in fetal lambs[10,11]. This baroreceptor mediated heart rate response increases with gestational age[10]. A vagally mediated decrease in heart rate after hypoxic activation of arterial chemoreceptors is found in fetal lambs[11,12,13]. This chemoreflex is reported to be a robust component of fetal adaptation to hypoxia[12]. In contrast to adults, hypoxaemia is reported to abolish fetal breathing movements in fetal lambs[14,15]. In addition, a ventricular receptor (Bezold-Jarisch) reflex comparable to that observed in human adults is seen in late gestation fetal lambs[16]. This Bezold-Jarisch reflex was absent in immature and premature lamb fetuses[17]. Right atrial stretching (by volume expansion) resulted in a vagally mediated bradycardia, in immature, premature and term fetuses[17]. This bradycardia was more pronounced with increasing gestational age[17]. In other words, the Bainbridge reflex as observed in human adults was reversed in fetuses. To gain more insight into these autonomic reflexes, the autonomic cardiac response in fetuses to common conditions is further discussed after the next section.

Fetal autonomic development

Early in development the heart is beating in an autoregulatory manner while later during fetal maturation it is under neural regulation. Histological studies have shown the presence of developing autonomic nerves in the human heart at seven to eight weeks of gestation[18]. However, the presence of intracardiac nerves may not reflect functional innervation. Walker showed in vitro evidence for autonomic neuroeffector transmission in the human fetus at 16 to 17 weeks of gestation[19], which is no evidence of autonomic reflex mechanisms.
In lambs, adrenergic tone is already present during early fetal life and the sympathetic nervous system exhibits a sensitive response to stimuli that increases with gestational age[17,20]. The vagal tone on resting heart rate in the fetal lamb is low[17,20]. However, the parasympathetic system is capable of exerting a strong action on the fetal cardiovascular system when stimulated, in both premature and mature fetuses, although the capability

increases with gestational age[17,20]. It is important to realise that, although the autonomic nervous system influences cardiovascular control during fetal development, the sympathetic and parasympathetic contribution changes with maturation. In sheep studies, sympathetic blockade with propanolol had profound effect on heart rate in all fetuses regardless of gestational age[17]. Parasympathetic blockade with atropine had no effect on resting heart rate in preterm fetal sheep, while for term fetuses an increase in heart rate was found[17]. The sympathetic nervous system controlling the heart develops and becomes functional earlier than the parasympathetic control of the cardiovascular function[20]. Therefore, during intrauterine life the influence of the sympathetic system on cardiovascular functions dominates the vagal influence. After birth, the parasympathetic tone of the resting heart rate rises to adult levels while adrenergic tone decreases[13,17,20]. In human newborns a comparable change in sympathovagal balance in favour of the latter is seen after birth[21]. These changes can be explained by autonomic maturation and postnatal adaptation.
Fetal heart rate variability (HRV) reflects the autonomic nervous system activity. Therefore, the increase in vagal and sympathetic modulation during fetal development is reflected in an increase in fetal HRV during pregnancy as reported by many investigators[22].

Fetal autonomic response to oxygen deficiency

The initial phase of oxygen deficiency is hypoxaemia. The fetal response depends on the level of oxygenation. The first defence is increased effectivity of oxygen uptake. The second defence is reduced activity. Finally, in case of long-lasting hypoxaemia, a decrease in growth rate occurs. The fetus can handle a situation of controlled hypoxaemia for weeks. However, the development of organ systems may be affected and the fetus is expected to have less ability to handle acute hypoxia during labour[23].
If oxygen saturation decreases further the fetus may enter the hypoxia phase. When a fetus is suffering from hypoxia, chemoreceptors are activated. Chemoreceptor activation stimulates parasympathetic activity that causes bradycardia and α-adrenergic activity that causes selective peripheral vasoconstriction. Due to this selective vasoconstriction, the blood flow to peripheral tissues is reduced and blood is shifted towards the central organs (heart, brain and adrenals) and arterial blood pressure increases[24,25]. In addition, β-adrenergic activity increases fetal heart rate to maintain cardiac output and umbilical blood flow during hypoxia[23,25]. Furthermore, the fetal response to hypoxia is a surge of the stress hormones adrenalin and noradrenalin from the adrenals and the sympathetic nervous system which results in a further increase in fetal heart rate and arterial blood pressure[24]. This surge of adrenaline results in glycogenolysis and as a result anaerobic metabolism in the peripheral tissues occurs[26]. In this situation, the central, high-priority organs secure their blood supply of glucose and oxygen.
With increasing oxygen deficiency, fetal metabolic acidosis with anaerobic metabolism in the central organs may occur. In case of acidosis the fetus reacts with maximum activation of the sympathetic nervous system and further release of catecholamines from the adrenals[26,27]. In fact, the fetus depends on sympathetic activation to maintain

cardiovascular activity with the redistribution of blood flow and the utilization of glycogen stores in the liver and myocardium. In the brain, very little glycogen is stored and therefore the brain is dependent on glucose supplied from the liver[27]. This marked adaptation requires an adequate autonomic regulatory system securing optimal organ function. Catecholamines have the ability to counteract the direct neurological depressant effect of hypoxia on the fetal heart and brain function. Even a normal vaginal delivery causes very marked activation of the sympathetic system to support the function of the central organs and fetal metabolism[13]. When the fetal defence reaches its final stage, the central nervous system will no longer be able to regulate the cardiovascular system and fetal hypotension develops. Heart rate variability will be absent as the system collapses and brain damage and eventually fetal death will occur. During the final stage, bradycardia due to the direct depressant effect of hypoxia on myocardial function may occur[28].

Fetal behaviour

Important changes in fetal heart rate can occur due to alterations in fetal activity. From a gestational age of 7 weeks fetal movements can be observed[29]. In early pregnancy they occur randomly over time. From a gestational age of 23 weeks, body movements become clustered into rest-activity cycles[30]. In the second half of pregnancy, episodes of fetal motility and rest become increasingly associated with the specific parameters of fetal heart rate pattern and eye movements, finally resulting in fetal behavioural states. These behavioural states are fully developed after 34 weeks of gestation[31]. Four categories of behavioural states can be distinguished in human fetuses. These states are identified by the coincidence of specific combinations of fetal heart rate pattern with the presence or absence of general and eye movements during a period of at least three minutes[32]. The most commonly used classification of fetal behavioural states is the classification according to Nijhuis[32]. A short description of the four behavioural states is given below.

State 1F, quiet sleep or non-rapid eye movement (REM) sleep
During state 1F fetal body movements are absent or occur sporadically and eye movements are absent. Less demand is imposed on autonomic regulatory mechanisms and fetal heart rate is stable with a small oscillation bandwidth. Isolated accelerations can occur, strictly related to movements.

State 2F, active sleep or REM sleep
During state 2F repeated gross fetal body movements and continuous eye movements are present. There are rapid shifts in autonomic nervous system activity and as a result frequent accelerations and increased fetal HRV are seen.

State 3F, quiet awake
During state 3F gross body movements are absent and eye movements are continuously present. The fetal heart rate is stable, but with a wider oscillation bandwidth than during 1F. There are no accelerations.

State 4F, active awake
During state 4F, vigorous, continuous activity including many trunk rotations and continuous eye movements are present. The fetal heart rate is unstable due to rapid shifts in autonomic nervous system activity which result in large and long-lasting accelerations, frequently fused into a sustained tachycardia.

In term fetuses most of the time is spent in behavioural state 1F and 2F and the frequency of the occurrence of the state 3F and 4F has been found to be relatively low[33,34]. Since the registrations described in this thesis were restricted to sleep states, only the differences in autonomic cardiac regulation between both sleep states will be discussed in the next paragraph.

The sympathovagal balance of the autonomic nervous system changes with sleep state. In human adults, the sympathetic modulation was higher during REM sleep than during non-REM sleep[35]. This change in sympathovagal balance during active and quiet sleep corresponds to the results observed in human fetuses[36]. The increase in sympathetic modulation in active sleep can be explained by an increase in body movements since movements result in heart rate acceleration[30]. Since respiratory movements are inhibited during quiet sleep[15], increased RSA cannot account for the difference in sympathovagal balance.

Fetal autonomic response to uterine contractions

Barcroft first described the development of cardiovascular reflexes during umbilical cord occlusion in the fetus[37]. His studies led to the description of early, variable and late decelerations in human fetal heart rate[37]. Autonomic modulation, during these three types of decelerations, is briefly discussed in the next paragraphs.

Variable decelerations
Variable decelerations occur due to umbilical cord compression. Studies showed that in healthy fetal lambs, a fetal heart rate response to uterine contractions occurred only after the umbilical blood flow was reduced by at least 50%[38]. During short partial cord occlusion, no significant changes in fetal arterial pH or blood pressure occur and the resulting hypoxaemia leads to a variable deceleration in fetal heart rate[38]. This variable deceleration was abolished during parasympathetic blockade with atropine and is thus of chemoreceptor reflex origin and vagally mediated[38]. The deceleration during hypoxaemia is an important fetal adaptation mechanism that is believed to reduce myocardial work and oxygen requirement[39]. The changes in fetal heart rate vary with the magnitude of reduction in umbilical blood flow. Complete cord occlusion is accompanied by hypoxaemia and increased blood pressure and leads to prolonged variable deceleration of fetal heart rate that is the result of both chemoreceptor and baroreceptor activation[38,40]. The increase in blood pressure during complete cord occlusion is due to increased peripheral resistance. This increased peripheral resistance is due to both occlusion of the umbilical cord and sympathetically mediated peripheral vasoconstriction caused by

hypoxaemia[25]. During prolonged or frequent cord occlusion, the fetus has no time to recover from hypoxaemia. The fetal heart rate decreases during the occlusion and rises to above normal values after the occlusion (overshoot), this overshoot is probably due to decreased vagal and increased β-adrenergic tone as it occurs in the face of fetal acidosis or hypotension[38,39,41]. If hypoxia is severe and prolonged for at least three minutes, the initial vagal bradycardia is sustained by direct hypoxic myocardial depression[39]. In conclusion, the fetal heart rate responses to cord compression are dependent on the severity of reduction in umbilical blood flow and on the frequency and duration of cord compression. The chemo- and baroreceptor reflex are thus not only a component of fetal adaptation but are also an indicator of the presence of fetal hypoxaemia. The depth to which fetal heart rate falls is often related to the severity of the hypoxia[39]. In other words, shallow decelerations indicate a modest reduction in uteroplacental blood flow, and deep decelerations indicate severe reduction. Thus, a shallow deceleration in labour indicates a mild fall in fetal oxygen tension. Deep decelerations reflect profound, albeit transient, hypoxaemia. Whether the repeated hypoxia that is associated with decelerations in heart rate is benign depends on the fetal condition and placental reserve, and on the duration and frequency of the decelerations.

Late decelerations

In case of reduced fetal reserve, a reduction in oxygen supply due to reduced placental blood flow during a contraction may also cause the activation of chemoreceptors. This activation of chemoreceptors evokes a vagal and a sympathetic response[42]. The direct vagal response yields a cardiodecelerator effect. The direct sympathetic response leads to a β-receptor mediated cardioaccelerator effect and to increased cardiac contractility. This β-receptor response increases blood pressure. In addition, the sympathetic pathway leads to an α-receptor mediated increase in vascular resistance which also increases blood pressure. The increase in blood pressure is sensed by the baroreceptor that reacts with an increased afferent fire rate that is forwarded to both the sympathetic centre (inhibition) and the vagal centre (stimulation). The vagal centre responds with a cardiodecelerator effect. The net effect is a deceleration in heart rate that starts after the contraction has reached its peak[42]. This baroreceptor reflex activation is due to an increase in blood pressure as part of the cardiovascular adaptation to hypoxia. After the contraction, the sympathetic activation is maintained, causing tachycardia.

Early decelerations

The fetus also reacts to changes in its external environment. For example, fetal head compression during uterine contractions increases intracranial pressure and cerebral resistance, thus reducing cerebral perfusion and oxygen supply. This local hypoxaemia stimulates the vagus nerve and decreases fetal heart rate[38]. Once the contraction diminishes, cerebral flow will restore and the oxygen level in the blood will normalise. This will also restore vagal nerve fire rate and fetal heart rate will correspondingly return to baseline level. This cascade is seen on the cardiotocogram as early decelerations[43]. During the last phase of labour, this cascade can also cause marked vagally induced bradycardia.

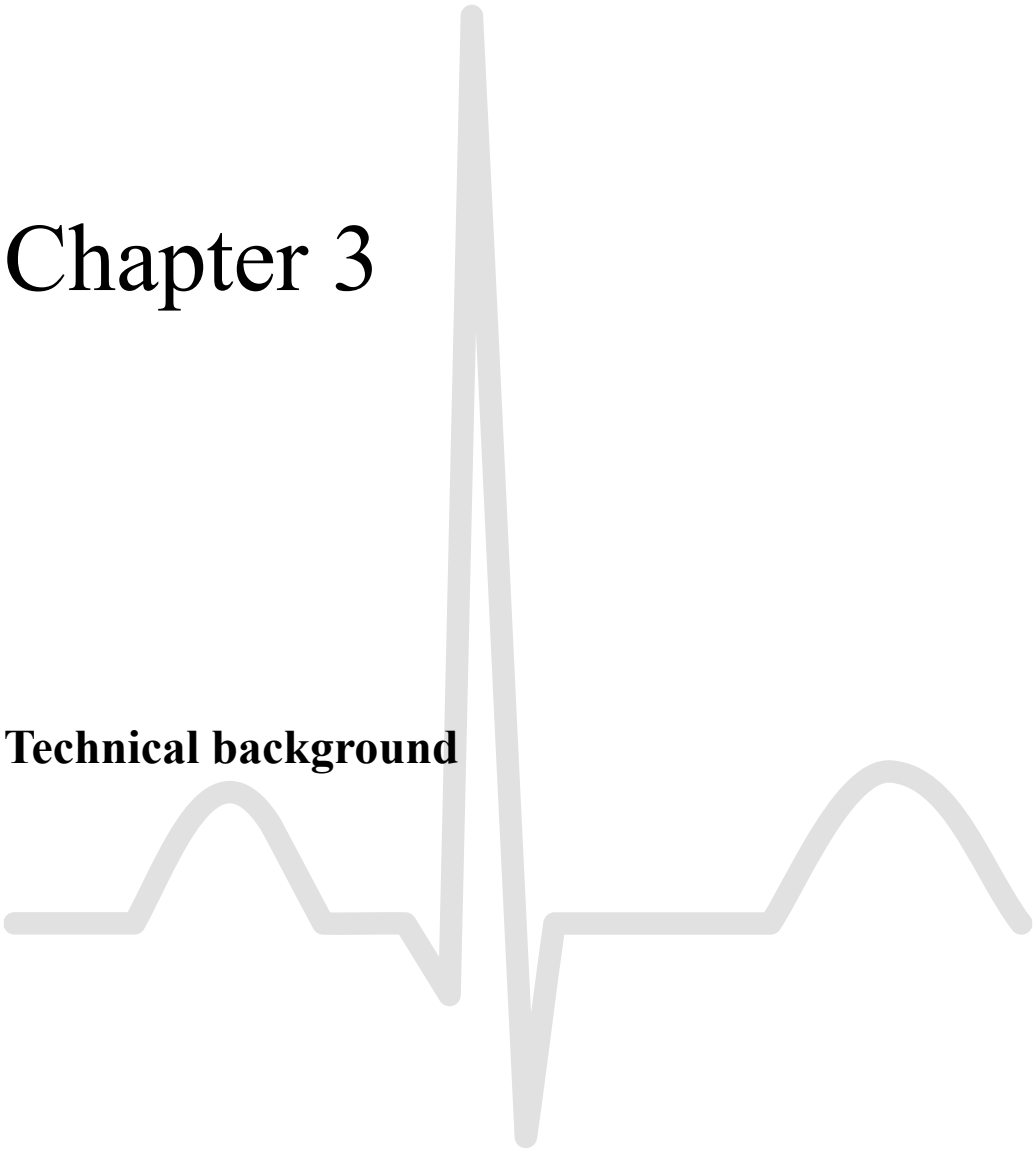
References

1. Berne RM, Levy MN. The autonomic nervous system and its central control. In Berne RM, Levy MN (eds). Physiology. Fourth edition. Mosby Inc., St Louis, USA 1998. Page 233-248.
2. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-1065.
3. Berne RM, Levy MN. Regulation of the heartbeat. In Berne RM, Levy MN (eds). Physiology. Fourth edition. Mosby Inc., St Louis, USA 1998. Page 379-399.
4. Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. Am J Physiol 1985;249:H867-H875.
5. van Ravenswaaij-Arts CMA. Heart rate variability. Physiology and clinical applicability in very preterm infants. PhD Thesis, Katholieke Universiteit Nijmegen, Nijmegen, 1993.
6. Brown DR, Yingling JD, Randall DC, Aral HM, Evans JM, Charles JB, Knapp CF, Raisch R, Ott CE. Angiotensin II does not contribute to rapid reflex control of arterial pressure. Am J Physiol 1991;261: R473-R477.
7. Divon MY, Yeh SY, Zimmer EZ, Platt LD, Paldi E, Paul RH. Respiratory sinus arrhythmia in the human fetus. Am J Obstet Gynecol 1985;151:425-428.
8. Groome LJ, Mooney DM, Bentz LS, Singh KP. Spectral analysis of heart rate variability during quiet sleep in normal human fetuses between 36 and 40 weeks of gestation. Early Hum Dev 1994;38:1-9.
9. Ferrazzi E, Pardi G, Setti PL, Rodolfi M, Civardi S, Cerutti S. Power spectral analysis of the heart rate of the human fetus at 26 and 36 weeks of gestation. Clin Phys Physiol Meas 1989;10 Suppl B:57-60.
10. Shinebourne EA, Vapaavuori EK, Williams RL, Heymann MA, Rudolph AM. Development of baroreflex activity in unanesthetized fetal and neonatal lambs. Circ Res 1972;31:710-718.
11. Itskovitz J, Rudolph AM. Denervation of arterial chemoreceptors and baroreceptors in fetal lambs in utero. Am J Physiol 1982;242:H916-H920.
12. Bennet L, Westgate JA, Liu YC, Wassink G, Gunn AJ. Fetal acidosis and hypotension during repeated umbilical cord occlusions are associated with enhanced chemoreflex responses in near-term fetal sheep. J Appl Physiol 2005;99:1477-1482.
13. Segar JL. Neural regulation of blood pressure during fetal and newborn life. In Polin RA, Fox WW (eds). Fetal and Neonatal Physiology. Third edition. WB Saunders, Philadelphia, USA 2003. Page 717-726.
14. Boddy K, Dawes GS, Fisher R, Pinter S, Robinson JS. Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep. J Physiol 1974;243:599-618.
15. Blanco CE. Maturation of fetal breathing activity. Biol Neonate 1994;65:182-188.
16. Nuyt AM, Segar JL, Holley AT, Robillard JE. Autonomic adjustments to severe hypotension in fetal and neonatal sheep. Pediatr Res 2001;49:56-62.
17. Nuwayhid B, Brinkman CR, Su C, Bevan JA, Assali NS. Development of autonomic control of fetal circulation. Am J Physiol 1975;228:337-344.
18. Pappano AJ. Ontogenetic development of autonomic neuroeffector transmission and transmitter reactivity in embryonic and fetal hearts. Pharmacol Rev 1997;29:3-33.
19. Walker D. Functional development of the autonomic innervation of the human fetal heart. Biol Neonate 1975;25:31-43.

20. Assali NS, Brinkman CR, Woods JR, Dandavino A, Nuwayhid B. Development of neurohumoral control of fetal, neonatal, and adult cardiovascular functions. Am J Obstet Gynecol 1977;129:748-759.
21. van Ravenswaaij-Arts C, Hopman J, Kollee L, Stoelinga G, van Geijn H. Spectral analysis of heart rate variability in spontaneously breathing very preterm infants. Acta Paediatr 1994;83:473-480.
22. Wakai RT. Assessment of fetal neurodevelopment via fetal magnetocardiography. Exp Neurol 2004;190 Suppl 1:S65-S71.
23. Parer JT. Fetal Cardiorespiratory Physiology. In Parer JT. Handbook of fetal heart rate monitoring. WB Saunders, Philadelphia, USA 2009. Page 48-70.
24. Hanson M, Kumar P. Chemoreceptor function in the fetus and neonate. Adv Exp Med Biol 1994;360:99-108.
25. Evers JL, de Haan J, Jongsma HW, Crevels AJ, Arts TH, Martin CB Jr. The preejection period of the fetal cardiac cycle. I. Umbilical cord occlusions. Eur J Obstet Gynecol Reprod Biol 1981;11:401-418.
26. Cohn HE, Sacks EJ, Heymann MA, Rudolph AM. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. Am J Obstet Gynecol 1974;120:817-824.
27. van Geijn HP, Visser GH. Beoordeling en interpretatie van het CTG tijdens de baring. In Nijhuis JG, Essed GG, van Geijn HP, Visser GH (eds). Foetale bewaking. Elsevier/Bunge, Maarssen, the Netherlands 1998. Page 75-94.
28. Sundstrom AK, Rosen D, Rosen KG. Fetal surveillance. Neoventa Medical, Goteborg, Sweden 2000. Page 1-38.
29. de Vries JI, Visser GH, Prechtl HF. The emergence of fetal behaviour. I. Qualitative aspects. Early Hum Dev 1982;7:301-322.
30. Pillai M, James D. The development of fetal heart rate patterns during normal pregnancy. Obstet Gynecol 1990;76:812-816.
31. Nijhuis IJ, ten Hof J, Nijhuis JG, Mulder EJ, Narayan H, Taylor DJ, Visser GH. Temporal organization of fetal behavior from 24-weeks gestation onwards in normal and complicated pregnancies. Dev Psychobiol 1999;34:257-268.
32. Nijhuis JG, Prechtl HF, Martin CB, Bots RS. Are there behavioural states in the human fetus? Early Hum Dev 1982;6:177-195.
33. Pillai M, James D. Behavioural states in normal mature human fetuses. Arch Dis Child 1990;65:39-43.
34. Mulder EJ, Visser GH, Bekedam DJ, Prechtl HF. Emergence of behavioural states in fetuses of type-l-diabetic women. Early Hum Dev 1987;15:231-251.
35. Busek P, Vanková J, Opavský J, Salinger J, Nevsímalová S. Spectral analysis of the heart rate variability in sleep. Physiol Res 2005;54:369-376.
36. David M, Hirsch M, Karin J, Toledo E, Akselrod S. An estimate of fetal autonomic state by time-frequency analysis of fetal heart rate variability. J Appl Physiol 2007;102:1057-1064.
37. Barcroft J. Fetal heart rate. The development of vascular reflexes. In Eskes TKAB, Longo LD (eds). Classics in obstetrics and gynecology: Innovative papers that have contributed to current clinical practice. Parthenon Publishing Group, Lancs, UK 1994. Page 25-46.
38. Itskovitz J, LaGamma EF, Rudolph AM. Heart rate and blood pressure responses to umbilical cord compression in fetal lambs with special reference to the mechanism of variable deceleration. Am J Obstet Gynecol 1983;147:451-457.

39. Westgate JA, Wibbens B, Bennet L, Wassink G, Parer JT, Gunn AJ. The intrapartum deceleration in center stage: a physiologic approach to the interpretation of fetal heart rate changes in labor. Am J Obstet Gynecol 2007;197:236.e1-11.
40. Ball RH, Parer JT. The physiologic mechanisms of variable decelerations. Am J Obstet Gynecol 1992;166:1683-1688.
41. Westgate JA, Bennet L, de Haan HH, Gunn AJ. Fetal heart rate overshoot during repeated umbilical cord occlusion in sheep. Obstet Gynecol 2001;97:454-459.
42. van der Hout-van der Jagt MB, Oei SG, Bovendeerd PH. Simulation of reflex late decelerations in labor with a mathematical model. Submitted for publication.
43. van der Hout-van der Jagt MB, Oei SG, Bovendeerd PH. A mathematical model for simulation of early decelerations in the cardiotocogram during labor. Med Eng Phys 2012;34:579-589.

Chapter 3



Technical background

Detection of fetal beat-to-beat heart rate

Before spectral analysis can be used for monitoring fetal autonomic cardiac modulation, fetal heart rate has to be available on a beat-to-beat basis. During labour, this can be obtained from direct fetal electrocardiogram (ECG) registration, measured by a scalp electrode on the fetal head. Antepartum, it can be obtained indirectly from fetal ECG measurements performed with skin electrodes placed on the maternal abdomen. The fetal heart is very small, compared to the maternal heart. Therefore, the amplitude of the fetal ECG waveform is 3 to 100 times smaller than that of the mother. Electrical measurements on the maternal abdomen provide a mixture of electrophysiological signals (including fetal and maternal ECG) and noise. The maternal ECG and maternal muscle activity largely obscure the fetal signal. In addition, the amplitude of the signal is reduced during the electrical conduction from the fetus to the maternal abdominal skin. Furthermore, the amplitude of the fetal component varies with the position of the measurement electrodes in relation to the position of the fetus in the uterus. To a smaller extent this is also influenced by the composition of the tissue between the fetus and the maternal skin. Finally, the development of the vernix caseosa electrically shields the fetus from its surroundings from around 28 to 32 weeks of gestation[1]. Extraction of fetal ECG from abdominal recordings is hence complicated, but not impossible. In the next paragraph it is discussed how the fetal ECG is extracted from abdominal measurements.

Antepartum fetal ECG detection

Antepartum fetal ECG recordings are performed non-invasively using self-adhesive electrodes positioned on the maternal abdomen. Before placing the electrodes the women's skin is prepared by gentle excoriation of surface skin cells and by cleaning the skin with alcohol in order to decrease the electrode-skin impedance. For the measurements in this thesis, 10 electrodes were used; eight measurement electrodes, one reference electrode and one ground electrode. The configuration is shown in Figure 3.1. Each of the eight abdominal signals is obtained from the voltage difference between a recording electrode and the reference electrode. To reduce the effect of power line interference, the electrode leads were shielded and a ground electrode was used.

By using multi-lead recordings, different leads can be combined to increase signal quality and recombination of leads can also be used to reconstruct the standard Einthoven leads, known from cardiology. Spreading the electrodes over the uterus, the chance of obtaining a relatively good fetal ECG signal in at least some of the electrodes is maximised. The abdominal signals are recorded and stored by the NEMO (Non-invasive Electrophysiologic Monitor for Obstetrics) system, shown in Figure 3.2.

This NEMO system is developed in the Máxima Medical Centre, in cooperation with the Eindhoven University of Technology and Maastricht instruments BV[2]. The system is approved by the Medical Technical Service Department of Máxima Medical Centre.

The first step in retrieving the fetal ECG is to filter the recorded signals to suppress high frequency noise, baseline drift and power line interference. The main component

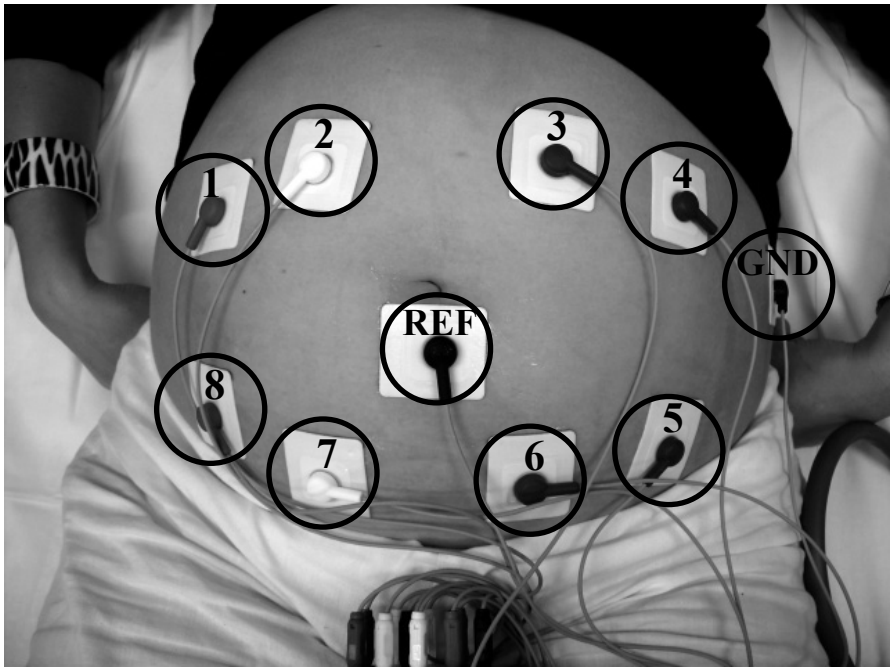


Figure 3.1. Electrode configuration for antepartum fetal ECG recording. REF: reference electrode. GND: ground electrode.

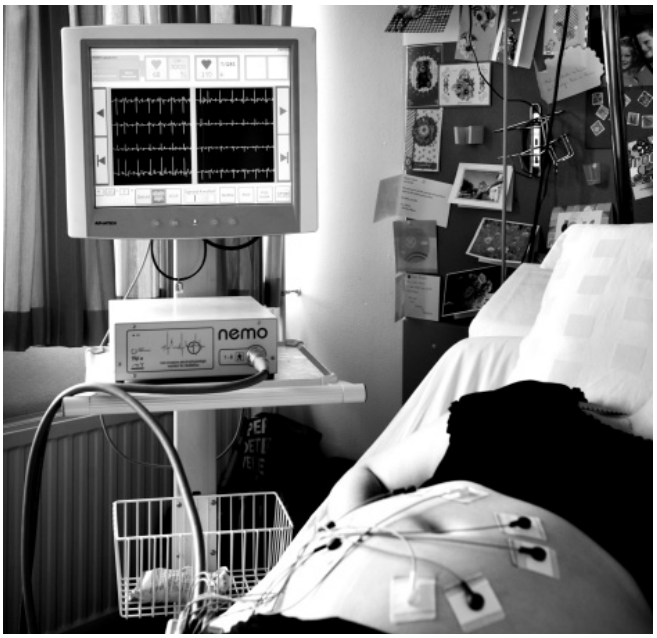


Figure 3.2. Prototype of the NEMO system.

interfering with the fetal ECG is the maternal ECG. The second step is therefore to remove the maternal ECG. This is done using a novel method that has been developed in a joint project of Máxima Medical Centre and Eindhoven University of Technology and that removes the maternal ECG by means of weighted averaging of maternal ECG segments[3]. For example, Figure 3.3 shows a filtered abdominal signal containing both maternal and fetal ECG. Figure 3.4 shows the signal after maternal ECG subtraction.

After subtracting the maternal ECG from each of the abdominal signals, eight presumed fetal ECG signals remain. The signal-to-noise ratio of these signals is enhanced by spatially combining the signals. R-peaks in the fetal ECG are then detected and used to create the fetal beat-to-beat heart rate signals.

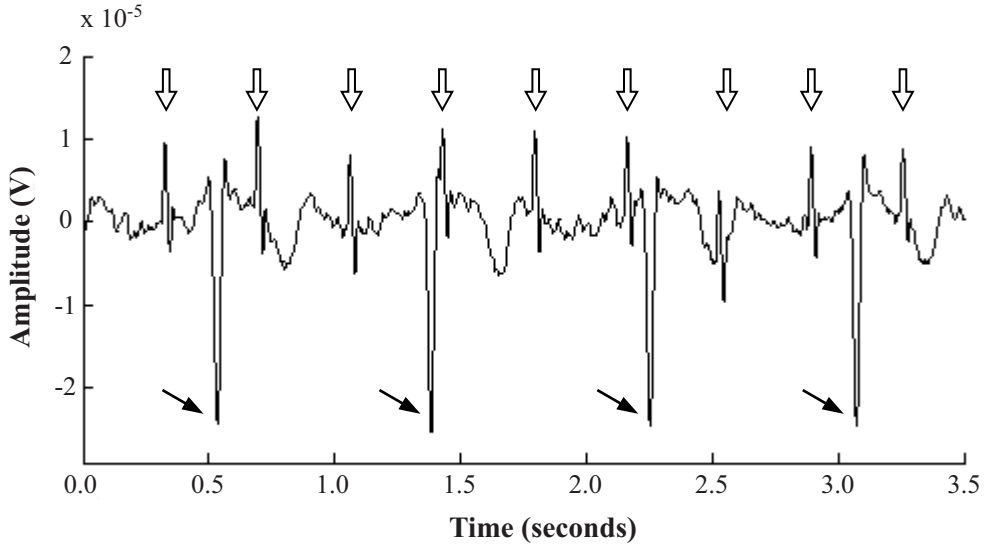


Figure 3.3. Filtered abdominal signal containing both maternal (↘) and fetal ECG (⇩).

Spectral analysis of fetal heart rate variability

Hon et al. described that administration of atropine to the mother abolished almost completely the variability in fetal heart rate, demonstrating the importance of the parasympathetic system regarding generation of heart rate fluctuations[4]. Invasive animal studies have proven that the vagus contributes to both fast and slow oscillations in heart rate while the sympathetic system contributes primarily to low frequent heart rate fluctuations[5]. After heart transplantation, complete cardiac denervation abolishes heart rate variability (HRV) completely[6]. Fetal HRV can be quantified by spectral analysis. Because fetal heart rate fluctuates under the influence of the autonomic nervous system, spectral estimates of fetal HRV reflect autonomic cardiac modulation.

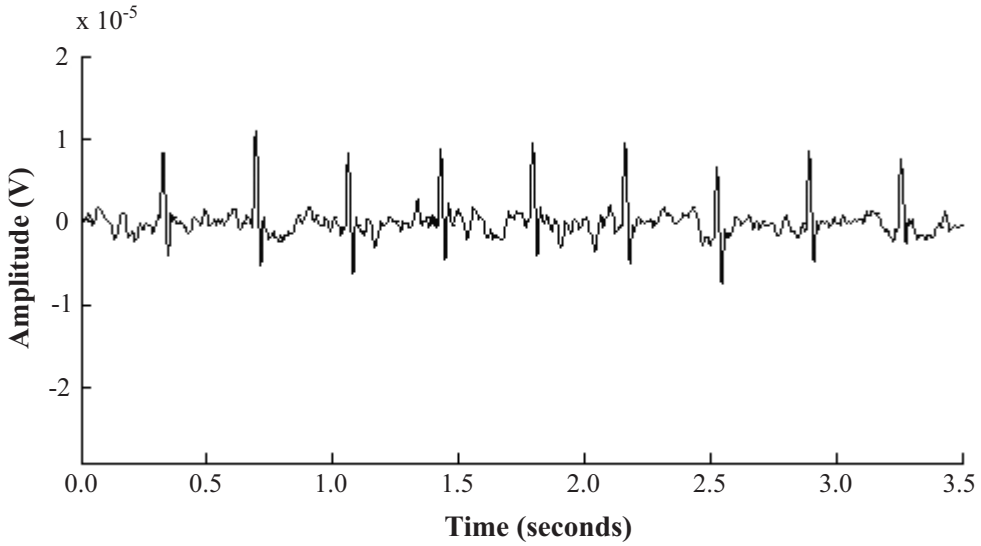


Figure 3.4. Filtered abdominal signal after subtraction of the maternal ECG.

Spectral analysis is the decomposition of a signal into sinusoids of different frequencies and amplitudes. Spectral analysis of HRV shows a characteristic spectrum in which a high and low frequency band can be distinguished. As impulses from the parasympathetic system are conveyed much faster than impulses from the sympathetic system, the sympathetic nervous system modulation is solely present in the low frequency (LF) band, while parasympathetic modulation is present in both frequency bands[7]. In human adults the LF band ranges from approximately 0.04 to 0.15 Hz and the high frequency (HF) band ranges from 0.15 to 0.4 Hz[8]. An example of a time-frequency spectrum of HRV for human adults is given in Figure 3.5.

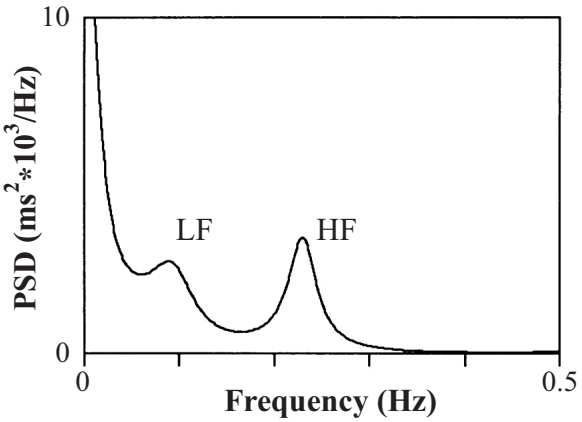


Figure 3.5. Example of a power spectrum of HRV for human adults. PSD: power spectral density.

For newborns it has been shown that the parasympathetic nervous system acts in a higher frequency range. Therefore, for newborns, the HF band has been defined as ranging from 0.4 to 1.5 Hz[9] and this definition is also accepted for studying HRV in fetuses.

Several methods can be used for calculation of the power in the LF and HF band. The Fourier transform defines the relationship between a signal in time-domain and its representation in the frequency-domain. Most studies concerning spectral analysis of fetal HRV used a Fourier transform[10,11,12]. For this thesis spectral information of fetal HRV was also obtained by calculating the Fourier transform. We chose this method because it is widely used, which makes it easier to compare our results with those obtained from other research groups.

Before performing spectral analysis, the beat-to-beat RR-intervals are pre-processed in a standardised way to increase reliability of spectral information[13]. To prevent incorrect RR-intervals from dominating the spectrum, possible incorrectly determined RR-interval values were corrected. An RR-interval was considered to be incorrect if it exceeded the range of 0.2 to 1.3 seconds (46 to 300 bpm) or deviated more than 12% from preceding successive RR-intervals[13]. These incorrect RR-intervals were removed from the dataset and replaced by linearly interpolating between the last preceding and the first succeeding correct RR-interval. Linear interpolation reduces the variability of the dataset, but this outweighs the error that is introduced by not correcting artefacts. To minimise the effect of artefact correction on the calculated spectral estimates, only signals with less than 5% artefact correction were included for analysis[14].

The Fourier transform requires sampled data to be equidistant. As RR-intervals are not equidistant they have to be resampled. The Nyquist criterion states that to obtain reliable spectral information, the signal has to be sampled at, at least twice the highest frequency of interest. Because the frequencies of interest range from 0.04 to 1.5 Hz, data were chosen to be resampled at 4 Hz. To avoid aliasing, the frequency of resampling must be higher than the instantaneous heart rate. The next step is eliminating the direct current (DC) offset from the signal by subtracting the signal's mean. The DC-offset causes very high power at 0 Hz in the frequency-domain, which leaks into neighbouring bins. Due to subtracting the signal's mean in time-domain, the 0 Hz peak is removed. According to the Nyquist criterion, the window should at least contain twice the wavelength of the lowest frequency of interest (0.04 Hz) and the Fourier transform requires 2^n samples. Because the rapidly fluctuating fetal autonomic system results in non-stationarity of the fetal heart rate signal, the minimal reliable window width of 64 seconds was chosen. Due to the fact that the data set that is used in the calculation of the spectrum is finite, leakage of power into other frequency bins may occur in the spectrum due to discontinuities at each side of the window (spectral leakage). To reduce spectral leakage the windowed signal is multiplied with a triangle (Parzen).

The signal is now ready for Fourier transform. To calculate the power spectrum of the pre-processed RR-series, 256-point Fourier transforms were calculated for partly overlapping, intervals of 64 seconds, which were shifted every 0.25 seconds. Hence,

after 64 seconds of RR data, spectral values are provided every 0.25 seconds. Besides calculating the absolute spectral power of fetal HRV in the specified frequency bands, normalised values were calculated by dividing LF and HF power by total power (0.04-1.5 Hz). After calculating the Fourier transform, corrections were made for the applied window functions[15]. Absolute spectral power data are given in arbitrary units or squared (milli) seconds; normalised spectral power data have no units.

References

1. Oostendorp TF, van Oosterom A, Jongsma HW. The effect of changes in the conductive medium on the fetal ECG throughout gestation. Clin Phys Physiol Meas 1989;10 Suppl B:11-20.
2. Peters CHL. Time-scale analysis of antepartum fetal heart rate variability. PhD Thesis, Eindhoven University of Technology, Eindhoven, 2011.
3. Vullings R. Non-invasive fetal electrocardiogram: analysis and interpretation. PhD Thesis, Eindhoven University of Technology, Eindhoven, 2010.
4. Hon EH, Bradfield AH, Hess OW. The electronic evaluation of fetal heart rate. The vagal factor in fetal bradycardia. Am J Obstet Gynecol 1961;82:291-300.
5. Chess GF, Tam RM, Calaresu FR. Influence of cardiac neural inputs on rhythmic variations of heart period in the cat. Am J Physiol 1975;228:775-780.
6. Fallen EL, Kamath MV, Ghista DN, Fitchett D. Spectral analysis of heart rate variability following human heart transplantation: evidence for functional reinnervation. J Auton Nerv Syst 1988;23: 199-206.
7. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213: 220-222.
8. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-1065.
9. Rosenstock EG, Cassuto Y, Zmora E. Heart rate variability in the neonate and infant: analytical methods, physiological and clinical observations. Acta Paediatr 1999;88:477-482.
10. Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Valimaki IA, Rosen KG, Ekholm EM. Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. BJOG 2005;112:418-423.
11. Chung DY, Sim YB, Park KT, Yi SH, Shin JC, Kim SP. Spectral analysis of fetal heart rate variability as a predictor of intrapartum fetal distress. Int J Gynaecol Obstet 2001;73:109-116.
12. Rantonen T, Ekholm E, Siira S, Metsala T, Leino R, Ekblad U, Välimäki I. Periodic spectral components of fetal heart rate variability reflect the changes in cord arterial base deficit values: a preliminary report. Early Hum Dev 2001;60:233-238.
13. Peters CH, ten Broeke ED, Andriessen P, Vermeulen B, Berendsen RC, Wijn PF, Oei SG. Beat-to-beat detection of fetal heart rate: Doppler ultrasound cardiotocography compared to direct ECG cardiotocography in time and frequency domain. Physiol Meas 2004;25:585-593.
14. Peters C, Vullings R, Bergmans J, Oei G, Wijn P. The effect of artifact correction on spectral estimates of heart rate variability. Conf Proc IEEE Eng Med Biol Soc 2008:2669-2672.
15. Bolderdijk AM. Fetal heart rate variability obtained from abdominal recordings: a longitudinal patient study. Master Thesis, Eindhoven University of Technology, Eindhoven, 2008.

Chapter 4

Spectral analysis of fetal heart rate variability for fetal surveillance: review of the literature

J.O.E.H. van Laar, M.M. Porath, C.H.L. Peters and S.G. Oei

Published: Acta Obstetricia et Gynecologica Scandinavica 2008;87:300-306

Abstract

Background: Cardiotocography has a poor diagnostic value in detecting fetal acidosis. Spectral analysis of fetal heart rate variability can be used to monitor the fetal autonomic nervous system.

Objective: To determine the value of spectral analysis for fetal surveillance.

Methods: A systematic search was performed in the electronic databases CENTRAL (the Cochrane library; 2007, Issue 3), PUBMED and EMBASE up to May 2007. Articles that described spectral analysis of human fetal heart rate variability and compared the energy in spectral bands with blood-gas values obtained by funipuncture or from the umbilical cord immediately postpartum were included.

Results: Six studies met the inclusion criteria. The included studies were heterogeneous, various methods of spectral analysis and different frequency bands were used and the outcome measures varied. Five out of six studies showed a decrease in spectral energy in the low frequency (LF) band in case of fetal distress. An extremely low LF power had a sensitivity of 97.5% and a specificity of 86.1% to detect fetal distress.

Conclusions: Spectral analysis could be a promising method for fetal surveillance. Larger prospective studies are needed to determine the exact diagnostic value of spectral analysis. For further research, standardisation of spectral analysis is recommended. Studies should focus on real-time monitoring.

Background

Fetal asphyxia is associated with severe perinatal morbidity and mortality[1,2,3]. The aim of fetal monitoring is to enable the obstetrician to intervene promptly in case of fetal hypoxemia before irreversible damage develops.

The standard method of fetal monitoring, the cardiotocogram (CTG), could not realise this goal. First, since CTG data are interpreted by the physician based on visual pattern recognition, the inter- and intraobserver variability is high[4]. Second, although the CTG has a high sensitivity, poor specificity of this method results in increased rates of unnecessary operative vaginal delivery and caesarean section without noticeable improvement of fetal outcome[5]. Therefore, additional information is needed to obtain objective information about the fetal condition. Fetal scalp blood sampling and ST-waveform analysis of the fetal electrocardiogram (STAN®) are examples of those methods, but have certain drawbacks. Both methods can only be applied during labour after membranes have ruptured and they are more or less invasive.

Fetal heart rate variability is reported to be an important CTG parameter in the assessment of fetal condition[6,7,8]. Normal fetal heart rate variability is a reliable indicator of fetal wellbeing irrespective of the heart rate pattern[7], and decreased fetal heart rate variability is associated with fetal acidosis, low Apgar score and perinatal death[7,8]. During fetal hypoxia, changes in autonomic nervous system activity result in changes in fetal heart rate variability[9]. Therefore, additional information might be obtained by using spectral analysis of fetal heart rate variability. Spectral analysis determines the energy in specific frequency components of heart rate variability. The low frequency (LF) component reflecting baroreceptor reflex activity is sympathetically and parasympathetically mediated, and the high frequency (HF) component is associated with respiration and parasympathetic nerve activity[10]. The ratio of the low frequency and high frequency powers (LF/HF) provides a marker of the sympathovagal balance in the control of heart rate[11,12]. Since the fetal heart rate fluctuates under the influence of centrally mediated changes in the sympathetic and parasympathetic tone[10], quantifying the variations in heart rate by spectral analysis can be used to monitor autonomic nervous system activity.

The objective of the current review is to determine the diagnostic value of spectral analysis of heart rate variability, performed on the human fetus, to detect fetal hypoxemia or acidosis.

Methods

Inclusion criteria

All published studies that described spectral analysis of heart rate variability of the human fetus and compared spectral energy in specific frequency bands with blood-gas values, obtained by funipuncture or from the umbilical cord immediately postpartum, were included in the study. Participants of interest were human fetuses, antepartum and

intrapartum. The outcome measures of interest were blood-gas values in the umbilical vessels (pH, pO_2, base excess or base deficit).

Search

A systematic search was performed in the electronic databases CENTRAL (the Cochrane library; 2007, Issue 3), PUBMED and EMBASE up to May 2007. The study language was restricted to English. The following keywords were used: spectral analysis, frequency analysis, heart rate variability, acidosis, asphyxia, fetal blood, fetal distress, hypoxemia, fetal hypoxia and fetal monitoring (if appropriate, MeSH terms were used). In addition, references of selected and related articles were searched.
Inclusion assessment and data extraction were performed by two independent review authors. There were no disagreements regarding inclusion or data extraction. After inclusion, the quality of the included studies was evaluated.

Results

Our search identified 106 articles for potential inclusion. Of these articles, 6 studies fulfilled the inclusion criteria. Characteristics of the included articles are shown in Table 4.1. Quality assessment of the included studies is shown in Table 4.2. The studies were published between 1999 and 2006. All studies were prospective cohort studies[13,14,15,16,17,18]. A total of 527 fetuses (range 3 to 334) were described. Two studies performed their measurements antepartum[14,16] and four intrapartum[13,15,17,18].

Antepartum studies

Both antepartum studies used Doppler ultrasound to obtain fetal heart rate on a beat-to-beat basis, and used an autoregression method for spectral analysis[14,16]. Umbilical vein pO_2 and pH were determined in blood collected by funipuncture or after elective caesarean section[14,16]. Both studies examined the LF band, which was defined as 0.06 to 0.31 Hz[14,16]. Ohta et al. studied 26 growth retarded fetuses, corrected for gestational age, and found that the LF power was positively associated with pO_2 and pH in the umbilical vein[16]. This was in agreement with Suzuki et al., who found that average LF power was significantly less in growth restricted fetuses with an umbilical venous $pO_2 < 20$ mmHg compared to normal fetuses and growth restricted fetuses without hypoxemia[14].

Intrapartum studies

The intrapartum studies performed measurements during labour, collected cord arterial blood and measured the pH[13,15,18] or base deficit[17] values after delivery. Bandwidths used for LF and HF bands differed between studies, as well as duration of recordings and time interval between spectral measurements and fetal blood collection (Table 4.1). Various cut-off points for fetal distress were used.

All included studies except Salamalekis et al.[18] demonstrated that spectral energy in the LF band decreased in case of fetal hypoxemia or acidemia. Siira et al. found that during

Table 4.1. Characteristics of included articles

Author	Number fetuses	GA (weeks)	Spectral analysis	Fetal heart rate	VLF (Hz)	LLF (Hz)	LF (Hz)	MF (Hz)	HF (Hz)	LF/ HF	Outcome measures and cut-off values	Timing measure-ment	Duration measure-ment	Duration RR segment data	Time lag recording and blood-gas
Ohta	26	20-38	Auto-regression	Ultra-sound			0.06-0.31				Δ pO_2 and Δ pH (umbilical vein)	Antepartum	$\geq$ 30 min	200 beats	Immediately
Suzuki	3	29-31	Auto-regression	Ultra-sound			0.06-0.31				$pO_2 < 20$ mmHg and pH $\geq$ 7.2 (umbilical vein)	Antepartum	24 h	10 min	Immediately
Rantonen	14	35-40	Fast Fourier transform	Scalp elec-trode			0.03-0.07	0.07-0.13	0.13-1.0		BD 8-12 mmol/l (umbilical artery)	Intrapartum	15 min	2 min	Median 2 h (range: 1-8 h)
Chung	76		Fast Fourier transform	Ultra-sound	< 0.04		0.04-0.15		0.15-0.4	+	pH < 7.15 and BD > 8 mmol/l (umbilical artery)	Intrapartum			2 h
Siira	334	$\geq$ 36	Fast Fourier transform	Scalp elec-trode			0.04-0.15		0.15-1.0	+	pH < 7.05 (umbilical artery)	Intrapartum	Last hour delivery	2 min	Median 4 min (95% CI: 1-9 min)
Salamalekis	74	> 37	Wavelet	Ultra-sound	< 0.04	0.04-0.08	0.08-0.15		> 0.15		pH < 7.2 (umbilical artery)	Intrapartum	Second stage labour		Immediately

GA: gestational age, VLF: very low frequency, LLF: low low frequency, LF: low frequency, MF: mid frequency, HF: high frequency, BD: base deficit.

Table 4.2. Quality assessment included studies

Included studies	Ohta	Suzuki	Rantonen	Chung	Siira	Salamalekis
Study design						
Cohort	X	X	X	X	X	X
Case-control						
Adequate description in-exclusion criteria						
Yes	X	X	X		X	X
No				X		
Participant sampling						
Consecutive						
Non-consecutive						
Unclear	X	X	X	X	X	X
Data sampling						
Prospective	X	X	X	X	X	X
Retrospective						
Adequate description of spectral analysis						
Yes	X	X	X	X	X	X
No						
Valid outcome measure						
Yes	X	X	X	X	X	X
No						
Fetal heart rate obtained beat-to-beat						
Yes	X	X	X		X	
No				X		X
Confounding variables						
Yes						
No						
Unclear	X	X	X	X	X	X
Clear definition fetal distress						
Yes		X	X	X	X	X
No	X					
Clinical data available as in clinical practice						
Yes	X	X	X	X	X	X
No						
Uninterpretable/missing results reported						
Yes				X	X	X
No	X	X	X			
Withdrawals explained						
Yes						
No						
Unclear	X	X	X	X	X	X

the last hour of labour LF heart rate variability initially increased, but near delivery decreased in acidotic fetuses with an arterial pH < 7.05 compared to control fetuses with a pH ≥ 7.05[13]. Rantonen et al. used a mid frequency (MF) band from 0.07 to 0.13 Hz. Spectral energy in the MF band was significantly lower in fetuses with an arterial base deficit of 8 to 12 mmol/l compared to fetuses with a normal base deficit value of < 8 mmol/l[17]. Since the range of their MF band was included in the LF band in the other studies, the observed results were comparable. Salamalekis et al. found an increased LF energy in cases with an arterial pH < 7.20 compared to control fetuses with a pH > 7.20[18].

Chung et al. was the only study that determined cut-off values for clinical management. According to Chung, a LF value ≤ 0.0013 was a good predictor of fetal acidemia with a sensitivity of 97.5% and a specificity of 86.1%[15]. The likelihood ratio (LR) for an abnormal test was 7.0 and the LR for a normal test 0.03[15].

Changes in energy in the HF band resembled the changes in LF energy to a lesser extent. Apart from Salamalekis et al., all studies showed a decrease in HF energy in case of fetal distress[13,15,17]. Salamalekis et al. found an increased HF energy in cases with an arterial pH < 7.20 compared to controls with a pH > 7.20[18].

Chung et al. and Salamalekis et al. also calculated spectral energy in the very low frequency (VLF) band < 0.04 Hz. Both showed a significant increase in VLF energy in case of fetal distress[15,18]. Specificity to detect fetal acidosis was higher for the VLF power spectrum than for the LF power spectrum[15].

Discussion

Complete spectral information of heart rate variability is only reliable if the heart rate is acquired on a beat-to-beat basis[19]. Fetal heart rate was determined from direct fetal electrocardiogram (ECG) signals measured with a scalp electrode in two studies[13,17], and from Doppler ultrasound cardiotocographic signals in four studies[14,15,16,18]. It is clear that beat-to-beat fetal heart rate can be obtained from RR-intervals calculated from direct ECG signals. Although it is feasible to derive beat-to-beat fetal heart rate from Doppler ultrasound[14,16], Chung et al.[15] and Salamalekis et al.[18] obtained an averaged fetal heart rate.

Doppler ultrasound data are suitable for spectral analysis, even if data are not available on a beat-to-beat basis. However, spectral information is only reliable for frequency smaller than half the frequency at which averaging takes place. Consequently, the spectral information that standard Doppler ultrasound CTG recordings provide is limited to the LF domain (< 0.15 Hz). Therefore, the average fetal heart rate can be used to determine spectral energy in the low frequency band but not in the high frequency band. This makes the results considering the HF data shown by Chung et al.[15] and Salamalekis et al.[18] questionable.

Studies chose spectral bands based on fetal animal or human adult studies. Since the human fetus has a different heart rate and a different pattern of breathing movements, these spectral bands may not be perfectly chosen. As sympathetic and parasympathetic blockade reported in animal studies[10], cannot be performed on human fetuses, the exact spectral bands useful for fetal monitoring remain unknown. This does not mean that spectral analysis cannot be used for fetal surveillance, however, for further research, agreement on the LF and HF bands is recommended.

We chose the umbilical cord blood-gas as the outcome of interest in this review since abnormal blood-gas is an objective parameter of fetal wellbeing and the most important prognostic risk factor for severe neonatal morbidity and mortality[20].

Since the included studies were too heterogeneous, it was not possible to pool the results. Despite differences in the characteristics of studied fetuses, definition of spectral bands, methodology of spectral analysis and outcome measures used, all studies except Salamalekis et al.[18] demonstrated that spectral energy in the LF band decreased in case of fetal hypoxemia and acidemia. The observed decrease in LF energy in case of fetal distress may seem to be at variance with the study of Salamalekis et al. and some animal studies. Salamalekis et al. showed a significant increase in LF energy in the group of fetuses with an arterial pH < 7.20 (mean pH 7.12 ± SE 0.01)[18]. For example, Yu et al. showed an increase in spectral energy in the LF band during mild and moderate hypoxemia in fetal lambs[21].

These observed differences might be due to differences in the severity of fetal distress in the included studies. The antepartum studies used umbilical venous blood pO_2, and in the intrapartum studies, the umbilical artery pH cut-off value varied between 7.05 and 7.20. One study used a base deficit value of 8 to 12 mmol/l. An arterial pH just below 7.20, as used by Salamalekis et al., points out that the fetal distress was mild and the arterial pH in the study of Yu et al. did not change throughout the experiments. Our hypothesis is supported by Dalton et al., who reported that in fetal lambs, after an initial rise of fetal heart rate variability during mild fetal distress, fetal heart rate variability decreases when the fetus deteriorates and develops acidemia[22]. The primary outcome should be metabolic acidosis, defined as a pH < 7.05 and a base deficit > 12 mmol/l in the umbilical cord artery because this indicates severe fetal compromise which is associated with major neonatal morbidity[20,23,24].

Siira et al. also found an initial increase in total, LF and HF heart rate variability that decreased in acidotic fetuses near delivery compared to control fetuses[13]. The initial increase in LF was accompanied by an increased LF/HF ratio[13]. This was consistent with Min et al. who showed an increase in total, LF and HF power and LF/HF ratio in hypoxemia compared with baseline state in fetal sheep[25]. Both studies stated that increased LF power and LF/HF during hypoxemia reflected increased sympathetic activity[13,25]. This increased activity of the cardiac autonomic nervous system could probably be a normal response to stress. This is similar to the finding that in a healthy fetus the LF and HF power rises during uterine contractions[26], representing an activation of the autonomic

nervous system to compensate for hypoxic stress due to uterine contractions.

In the human fetus, an increase in total heart rate variability during labour is mainly due to an increase in LF heart rate variability[13]. This was thought to be caused predominantly by sympathetic activation because in fetuses the sympathetic system predominates due to a rather immature vagal nervous system[13,27]. This is at variance with the study of Yu et al. They showed that mild stress in fetal sheep induced an increase in heart rate variability and LF power, which was abolished by vagal blockade, whereas sympathetic blockade had no effect[21]. Therefore, it was thought that during mild fetal stress, heart rate variability was mainly modulated by changes in cardiac vagal tone[21]. However, there was also a rise in fetal heart rate in parasympathetically blocked fetuses and a greater fall in fetal heart rate in sympathetically blocked fetuses during mild stress pointing to increased sympathetic activity probably caused by increased secretion of catecholamines[21]. This might also apply to human fetuses, however, as the concordance between animal studies and clinical studies is known to vary[28], the exact mechanism in human fetuses is unknown.

One study used STAN® data and found that a relative change in LF/HF ratio of fetal heart rate variability of > 30% in relation to a significant ST-event was associated with newborn metabolic acidosis[29]. Siira et al. found an increased LF/HF ratio in the acidotic group during the whole study period, which might reflect changes in sympathetic activity[13]. This is in accordance with Pincus et al. who also showed a shift towards LF in case of fetal acidosis[30]. However Chung et al. found no change in LF/HF ratio[15]. The observed differences in sympathovagal balance could be due to the different frequency bands used, due to differences in severity of fetal acidosis, or due to the questionable method of HF power measurement by Chung et al.

In those studies examining total spectral energy, a decrease in total spectral energy was found in case of fetal distress. This is similar to the results of Li et al., who reported that powers of fetal heart rate variability in all frequency-domains were lower in case of low approximate entropy which was associated with fetal hypoxemia, acidosis and decreased base excess[31].

In human adults, the VLF band (0.003-0.04 Hz) is associated with temperature regulation and humoral systems[11]. For clinical practice, it is a major drawback that changes in the VLF band appear after a delay of almost 6 min. Therefore, the high specificity of an increased VLF energy to detect fetal acidosis found by Chung et al.[15] is probably clinically less applicable.

The LF and HF spectral power can be expressed as absolute or normalised units. In healthy human adults, sympathetic excitation leads to tachycardia, which is accompanied by a reduction in the total power, while in case of vagal excitation the reverse is true[32]. If absolute units are used, the changes in total power influence both LF and HF power in the same direction[32]. Therefore, for human adults normalisation is recommended to make it possible to detect relative changes in LF or HF power[11], which could be masked

by changes in total power. Li et al. showed an increased power over the entire frequency range and in relative power in the LF range combined with a decrease in relative power in the HF range in case of acute hypoxemia in fetal sheep[33]. They stated that relative proportions of power spectrum of fetal heart rate could be more effective predictors of early fetal distress, since it reflects the changes in all frequency ranges[33]. None of the six included studies used normalised values. As the effect of some domains is ignored using the absolute values as an index of autonomic activity, for further research on human fetuses the use of normalised values is recommended.

The decrease in LF, HF and total power seen in the included studies during fetal compromise may represent a sign of decompensation of the fetal circulatory system due to loss of autonomic control or an inability of the fetal heart to respond. Chung et al. hypothesised a shift from HF to LF during fetal distress with an eventual loss of autonomic balance, which leads to fetal death[15]. This is in agreement with Oppenheimer et al., who demonstrated that, the increased LF/HF seen in the healthy fetus as a response to uterine contractions, was not seen in the severe acidotic fetus[34], suggesting that major acidosis resulted in loss of the central autonomic cardiovascular control. Divon et al. showed similar results, since they reported a reduced high frequency respiratory sinus arrhythmia in asphyxiated term neonates[35].

In most of the clinical human adult studies, a reduced responsiveness to an excitatory stimulus was seen in case of different pathophysiological conditions[36]. In advanced cardiac failure, decreased heart rate variability was also associated with a complete autonomic withdrawal and poor prognosis[11].

As an extremely low LF power was a good predictor of severe fetal acidosis with a sensitivity of 97.5% and a specificity of 86.1%[15], the diagnostic value of spectral analysis to detect fetal acidosis seems promising. However, the number of acidotic fetuses in the included studies was too small to determine clinical applicability. Considering the use of cut-off values, it should be taken into account that heart rate variability has a large inter-individual variation. For example, since fetal heart rate variability is positively associated with gestational age and negatively associated with fetal birthweight[13]. Further, intra-individual fluctuations can occur due to changes in behavioural state[37] or due to diurnal rhythms[14]. Different cut-off points should probably be used for different sub-groups of patients. Apart from inter- and intraindividual variation, the use of cut-off values is only useful if the method used for spectral analysis is reproducible for others. Not only will frequency bands need to be standardised, but the pre-processing of the data and the spectral analysis itself need to be standardised.

Maturation of the fetal autonomic nervous system affects the haemodynamic response to stress. Since power in the LF and HF spectral bands increases with gestational age[16,38], longitudinal studies throughout gestation should be performed in order to follow changes in fetal heart rate variability during pregnancy and to determine from which gestational age the autonomic nervous system is mature enough that spectral analysis can be used for fetal monitoring.

Our results indicate that spectral analysis of fetal heart rate variability gives additional information on fetal condition. This hypothesis is supported by the study of Rantonen et al. who showed that the observed changes in spectral energy in cases with elevated cord arterial base deficit were apparent before any abnormalities were found in the cardiotocographic recordings[17]. The included studies performed spectral analysis off-line, whereas to increase clinical applicability, future research should focus on real-time spectral analysis.

Conclusions

This review indicates that spectral analysis of fetal heart rate variability could be a useful method for fetal monitoring. It seems that in the human fetus an increase in LF power during the first stage of fetal compromise points to sympathetic hyperactivity caused by stress. A decrease in LF power in severe fetal compromise might be due to cardiovascular decompensation. An extremely low LF power was a good predictor of severe fetal acidosis with a sensitivity of 97.5% and a specificity of 86.1%. For further research, standardisation of spectral analysis is recommended to increase reproducibility. Larger prospective studies are needed to determine the exact diagnostic value of spectral analysis for the identification of fetuses at risk for severe acidosis, and are needed to enhance our understanding of the fetal autonomic nervous system. For clinical applicability, research should focus on real-time spectral analysis.

References

1. de Haan M, Wyatt JS, Roth S, Vargha-Khadem F, Gadian D, Mishkin M. Brain and cognitive-behavioural development after asphyxia at term birth. Dev Sci 2006;9:350-358.
2. Victory R, Penava D, da Silva O, Natale R, Richardson B. Umbilical cord pH and base excess values in relation to adverse outcome events for infants delivering at term. Am J Obstet Gynecol 2004;191:2021-2028.
3. Martin-Ancel A, Garcia-Alix A, Gaya F, Cabanas F, Burgueros M, Quero J. Multiple organ involvement in perinatal asphyxia. J Pediatr 1995;127:786-793.
4. Nielsen PV, Stigsby B, Nickelsen C, Nim J. Intra- and inter-observer variability in the assessment of intrapartum cardiotocograms. Acta Obstet Gynecol Scand 1987;66:421-424.
5. Alfirevic Z, Devane D, Gyte GM. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour (Review). Cochrane Database Syst Rev 2006.
6. Dawes GS, Moulden M, Redman CW. The advantages of computerized fetal heart rate analysis. J Perinat Med 1991;19:39-45.
7. Paul RH, Suidan AK, Yeh SY, Schifrin BS, Hon EH. Clinical fetal monitoring. VII. The evaluation and significance of intrapartum baseline FHR variability. Am J Obstet Gynecol 1975;123:206-210.
8. Rochard F, Schifrin BS, Goupil F, Legrand H, Blottiere J, Sureau C. Nonstressed fetal heart rate monitoring in the antepartum period. Am J Obstet Gynecol 1976;126:699-706.
9. van Ravenswaaij-Arts CM, Kollee LA, Hopman JC, Stoelinga GB, van Geijn HP. Heart rate variability. Ann Intern Med 1993;118:436-447.
10. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213: 220-222.
11. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-1065.
12. Cerutti S, Civardi S, Bianchi A, Signorini MG, Ferrazzi E, Pardi G. Spectral analysis of antepartum heart rate variability. Clin Phys Physiol Meas 1989;10:27-31.
13. Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Valimaki IA, Rosen KG, Ekholm EM. Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. BJOG 2005;112:418-423.
14. Suzuki T, Kimura Y, Murotsuki J, Murakami T, Uehara S, Okamura K. Detection of a biorhythm of human fetal autonomic nervous activity by a power spectral analysis. Am J Obstet Gynecol 2001;185:1247-1252.
15. Chung DY, Sim YB, Park KT, Yi SH, Shin JC, Kim SP. Spectral analysis of fetal heart rate variability as a predictor of intrapartum fetal distress. Int J Gynaecol Obstet 2001;73:109-116.
16. Ohta T, Okamura K, Kimura Y, Suzuki T, Watanabe T, Yasui T, Yaegashi N, Yajima A. Alteration in the Low-Frequency Domain in Power Spectral Analysis of Fetal Heart Beat Fluctuations. Fetal DiagnTher 1999;14:92-97.
17. Rantonen T, Ekholm E, Siira S, Metsalla T, Leino R, Ekblad U, Valimaki I. Periodic spectral components of fetal heart rate variability reflect the changes in cord arterial base deficit values: a preliminary report. Early Hum Dev 2001;60:233-238.

18. Salamalekis E, Hintipas E, Salloum I, Vasios G, Loghis C, Vitoratos N, Chrelias CH, Creatsas G. Computerized analysis of fetal heart rate variability using the matching persuit technique as an indicator of fetal hypoxia during labor. J Matern Fetal Neonatal Med 2006;19:165-169.
19. Peters CH, ten Broeke ED, Andriessen P, Vermeulen B, Berendsen RC, Wijn PF, Oei SG. Beat-to-beat detection of fetal heart rate: Doppler ultrasound cardiotocography compared to direct ECG cardiotocography in time and frequency domain. Physiol Meas 2004;25:585-593.
20. Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. Am J Obstet Gynecol 1997;177:1391-1394.
21. Yu ZY, Lumbers ER, Gibson KJ, Stevens AD. Effects of hypoxaemia on foetal heart rate, variability and cardiac rhythm. Clin Exp Pharmacol Physiol 1998;25:577-584.
22. Dalton KJ, Dawes GS, Patrick JE. Diurnal, respiratory, and other rhythms of fetal heart rate in lambs. Am J Obstet Gynecol 1977;127:414-424.
23. Goldaber KG, Gilstrap LC, Leveno KJ, Dax JS, McIntire DD. Pathologic fetal acidemia. Obstet Gynecol 1991;78:1103-1107.
24. Siggaard-Andersen O. An acid-base chart for arterial blood with normal and pathophysiological reference areas. Scand J Clin Lab Invest 1971;27:239-245.
25. Min SW, Ko H, Kim CS. Power spectral analysis of heart rate variability during acute hypoxia in fetal lambs. Acta Obstet Gynecol Scand 2002;81:1001-1005.
26. Romano M, Bifulco P, Cesarelli M, Sansone M, Bracale M. Foetal heart rate power spectrum response to uterine conraction. Med Biol Eng Comput 2006;44:188-201.
27. Assali NS, Brinkman CR, Woods JR, Dandavino A, Nuwayhid B. Development of neurohumoral control of fetal, neonatal and adult cardiovascular functions. Am J Obstet Gynecol 1977;129: 748-759.
28. Perel P, Roberts I, Sena E, Wheble P, Briscoe C, Sandercock P, Macleod M, Mignini LE, Jayaram P, Khan KS. Comparison of treatment effects between animal experiments and clinical trials: systematic review. BMJ 2006;334:197-200.
29. Siira S, Ojala T, Ekholm E, Vahlberg T, Blad S, Rosen KG. Change in heart rate variability in relation to a significant ST-event associates with newborn acidosis. BJOG 2007;114:819-823.
30. Pincus SM, Viscarello RR. Approximate entropy: a regularity measure for fetal heart rate analysis. Obstet Gynecol 1992;79:249-255.
31. Li X, Zheng D, Zhou S, Tang D, Wang C, Wu G. Approximate entropy of fetal heart rate variability as a predictor of fetal distress in women at term pregnancy. Acta Obstet Gynecol Scand 2005;84: 837-843.
32. Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: a tool to explore neural regulatory mechanisms. Br Heart J 1994;71:1-2.
33. Li X, Tang D, Zhou S, Zhou G, Wang C, Zhuang Y, Wu G, Shen L. Redistribution of power spectrum of heart rate variability during acute umbilical artery embolism and hypoxemia in late-gestation fetal sheep. Eur J Obstet Gynecol Reprod Biol 2004;114:137-143.
34. Oppenheimer L, Gruslin A, Mc Donald D, Dabrowski AR, Lachapelle S. Power spectral analysis (PSA) of fetal heart rate (FHR) in labor. Am J Obstet Gynecol 1993;168:342.
35. Divon MY, Winkler H, Yeh SY, Platt LD, Langer O, Merkatz IR. Diminished respiratory sinus arrhythmia in asphyxiated term infants. Am J Obstet Gynecol 1986;155:1263-1266.
36. Malliani A, Montano N. Current perspective. Heart rate variability as a clinical tool. Ital Heart J 2002;3:439-445.

37. Davidson SR, Rankin JH, Martin CB, Reid DL. Fetal heart rate variability and behavioral state: Analysis by power spectrum. Am J Obstet Gynecol 1992;167:717-222.
38. van Leeuwen P, Geue D, Lange S, Hatzmann W, Grönemeyer D. Changes in the frequency power spectrum of fetal heart rate in the course of pregnancy. Prenat Diagn 2003;23:909-916.

Chapter 5

Fetal autonomic response to severe acidaemia during labour

J.O.E.H. van Laar, C.H.L. Peters, R. Vullings, S. Houterman, J.W.M. Bergmans and S.G. Oei

Published: BJOG: An International Journal of Obstetrics and Gynaecology 2010; 117:429-437

Abstract

Objective: Spectral analysis of heart rate variability is used to monitor autonomic nervous system fluctuations. The low frequency component is associated with sympathetic and parasympathetic modulation and the high frequency component is associated with parasympathetic modulation. The objective was to study whether changes in low frequency or high frequency power of heart rate variability occur in case of fetal distress.

Design: Case-control study.

Setting: Obstetric unit of a tertiary-care teaching hospital.

Population: Twenty healthy human fetuses during labour at term of which ten had an umbilical artery pH < 7.05 (cases), and 10 had an arterial pH > 7.20 (controls) after birth.

Methods: Spectral information about fetal beat-to-beat heart rate, calculated from direct fetal electrocardiogram registrations, was obtained by using a short time Fourier transform.

Main outcome measures: Absolute power and normalised power in the low frequency and high frequency bands.

Results: No differences were found between fetuses with and without acidaemia in absolute low or high frequency power ($P = 0.2$ and $P = 0.3$ respectively). During the last 30 minutes of labour, acidaemic fetuses had significantly increased normalised low frequency power ($P = 0.01$) and decreased normalised high frequency power ($P = 0.03$) compared with non-acidaemic fetuses. These differences were not observed from 3 to 2 hours before birth ($P = 0.7$ and $P = 0.9$ respectively).

Conclusions: The autonomic nervous system of human fetuses at term responds adequately to severe stress during labour. Normalised low and high frequency power of heart rate variability might be able to discriminate between normal and abnormal fetal condition.

Introduction

Detection of fetal distress during labour is complex. The cardiotocogram (CTG), a simultaneous recording of fetal heart rate and uterine contractions, is the method used worldwide for fetal surveillance. Poor specificity of this method has resulted in increased rates of operative deliveries without a decrease in perinatal mortality or cerebral palsy[1]. It has been shown that during labour combined use of CTG and automatic ST-waveform analysis of the fetal electrocardiogram (ECG; STAN®, Neoventa Medical, Moelndal, Sweden) reduces the rates of severe metabolic acidosis at birth and instrumental vaginal delivery for fetal distress[2]. However, slow progressive deterioration of the CTG without pathological changes in ST-waveform (ST-events) has been reported as a cause of neonatal metabolic acidosis despite monitoring using STAN®[3]. Furthermore, STAN® remains dependent on the assessment of the CTG, which has a high inter- and intraobserver variability[4]. Although the CTG has a high sensitivity, ST-events occur at a similar frequency for normal and abnormal CTG patterns[5]. This illustrates the need for more detailed information on the fetal cardiovascular response to hypoxaemia.

Hypoxaemia activates the autonomic nervous system, which subsequently modulates beat-to-beat heart rate[6]. Spectral analysis is a method that can be used to detect and quantify these changes in heart rate objectively[7,8]. Spectral analysis decomposes sequential RR-interval series into a sum of sinusoids of different amplitudes and frequencies by the fast Fourier transform algorithm[6]. The power spectrum reflects the magnitude of heart rate variability (power) present at different frequency ranges[6]. Spectral power (variability) in the low frequency (LF) range is associated with sympathetic and parasympathetic nervous system modulation and spectral power (variability) in the high frequency (HF) range is associated with parasympathetic modulation[7]. This is because the fetal heart rate fluctuates under the influence of the sympathetic and parasympathetic nervous system. As impulses from the parasympathetic nervous system are conveyed much faster than impulses of the sympathetic nervous system, sympathetic modulation is solely present in the LF range while parasympathetic modulation is also present in the HF range[7,9]. In other words, sympathetic modulation of the fetal heart rate leads to slow oscillations while parasympathetic modulation also leads to fast oscillations. As spectral analysis evaluates oscillations in beat-to-beat fetal heart rate, it has the potential to monitor the autonomic nervous system modulation and may provide an early diagnostic tool for assessing fetal distress.

Previous studies have demonstrated that spectral power in the LF and HF ranges decreased in case of fetal hypoxaemia or acidaemia[10,11,12,13,14]. This was thought to be the result of immaturity or decompensation of the fetal autonomic nervous system. However, these studies used absolute values of LF and HF power, whereas changes in total power (total heart rate variability) influence LF and HF power in the same direction. Normalised values of LF and HF power seem more suitable for fetal monitoring because they detect relative changes, that cannot be masked by changes in total power[9]. Normalised LF (LFn) and normalised HF (HFn) power are calculated by dividing LF and HF power respectively by total power and represent the controlled and balanced behaviour of the two branches

of the autonomic nervous system[9]. We hypothesised that the autonomic cardiovascular control is functional in fetuses at term, and that LFn power would gradually increase in case of distress because of increased sympathetic nervous system modulation. The aim of our study was to compare spectral values in healthy and distressed fetuses during labour at term to determine whether differences in spectral values exist, which could be used in future research to improve fetal monitoring.

Methods

A case-control study was performed. Healthy fetuses of at least 36 weeks of gestation with intrapartum fetal ECG recordings, whose umbilical cord arterial and venous acid-base status was analysed immediately after delivery, were studied. Only good-quality fetal ECG recordings, free of ectopic beats and missing data, until at least 10 minutes before birth were included. Furthermore, only fetal ECG registrations from healthy mothers who experienced an uncomplicated pregnancy and did not use any medication, except oxytocin or epidural analgesia, were included. Pregnancies complicated by intrauterine growth restriction or fetal congenital anomalies were excluded. The controls (i.e. fetuses without acidaemia) were defined as fetuses with an umbilical arterial pH > 7.20 after birth. The included registrations were made in the Máxima Medical Centre, Veldhoven and were selected consecutively from the period January 2007 to August 2007. The cases (i.e. fetuses with acidaemia) were defined as having an umbilical artery pH < 7.05. These registrations were selected consecutively from the period January 2006 to December 2007. As a result of the strict inclusion and exclusion criteria only five fetuses with acidaemia could be included. In addition, five fetuses with acidaemia from the University Medical Centre Utrecht were selected consecutively from the period January 2001 to July 2002. Both hospitals are tertiary-care teaching hospitals.

Data acquisition and signal processing

A frequency-specific assessment of heart rate variability by spectral analysis is a well-established means of characterising autonomic cardiac control[7]. Our method has been described in more detail in previous studies[15,16]. The fetal ECG was recorded during delivery using a single-helix scalp electrode (Goldtrace™, Neoventa Medical, Moelndal, Sweden) and a maternal skin electrode. The scalp electrode was connected to a STAN S31® monitor (Neoventa Medical). The included registrations were analysed including accelerations and decelerations.

The STAN® device detected the R-peak location of each heart beat exactly, from the scalp ECG signal at a rate of 500 Hz. Although separate ECG waveforms can be aligned to calculate average fetal ECG waveforms to improve the signal quality of the waveform used for ST analysis, RR-intervals are provided on a true beat-to-beat basis. These beat-to-beat RR-interval data sets were stored on a PC hard disc and analysed off-line.

For spectral analysis a fast Fourier transform algorithm was used. Based on previous studies as well as the physiological range of fetal heart and respiratory movement rates the

following frequency bands were chosen: total frequency band: 0.04 to 1.5 Hz, LF: 0.04 to 0.15 Hz and HF: 0.4 to 1.5 Hz[16,17]. The Fourier transform is a mathematical method that transforms data from quantity (fetal heart rate) varying over time to amplitude (spectral power) varying over a range of frequencies. In other words, it performs the conversion of a function in the time-domain to the frequency-domain.

Before applying spectral analysis, the beat-to-beat RR-intervals are pre-processed in a standardised way to increase reliability of spectral information[15]. The Fourier transform requires sampled data to be equidistant. As RR-intervals are not equidistant they have to be resampled. The Nyquist criterion states that to obtain reliable spectral information, the signal has to be resampled at, at least, twice the frequency of the highest frequency of interest (1.5 Hz). Because the fast Fourier transform requires 2^n samples, data were resampled at 4 Hz. Because the rapidly fluctuating fetal autonomic system results in non-stationarity of the fetal heart rate signal, a minimum window length of 64 seconds was chosen. This window length was considered reliable because it included at least twice the wavelength of the lowest frequency of interest (0.04 Hz). The signal's mean was subtracted and to reduce the effect of discontinuities at each side of the window the signal was multiplied with a triangular window (Parzen)[15].

The signal is then ready for Fourier transformation. To calculate the power spectrum of the pre-processed RR-series, 256-point Fourier transforms were calculated for partly overlapping, intervals of 64 seconds, which were shifted every 0.25 seconds[15]. Hence, after 64 seconds, spectral values are provided every 0.25 seconds. Besides calculating the absolute spectral power of fetal heart rate variability in the specified frequency bands, normalised values were calculated by dividing LF and HF power respectively by total power. Spectral power data were given in arbitrary units. We refer to earlier papers for further details on our method of spectral analysis[15,16].

Statistical methods

For statistical analysis SPSS 12.0 (SPSS Inc., Chicago, IL, USA) was used. Fetal characteristics were tested with Student's *t* test (continuous variables) and Fisher's exact test (categorical variables). Significance was tested two-sided at an α-level of 0.05. For the last 30 minutes of labour, mean power in the LF, HF, LFn, HFn bands was calculated for intervals of 5 minutes. Values were calculated for 4 minutes overlapping providing one new value every minute for the preceding 5-minute continuous signal segment. These longitudinal mean 5-minute LF, HF, LFn, HFn power values were compared between fetuses with and without acidaemia using an analysis of variance (ANOVA) for repeated measures. In addition, to compare mean 5-minute LFn and HFn power longitudinally between fetuses with and without acidaemia during the first stage of labour, the repeated measures ANOVA was also performed for the 1-hour period from 3 to 2 hours before birth.

For all 20 fetuses good-quality ECG data were available until 9 minutes before birth. From four fetuses with acidaemia and five fetuses without acidaemia beat-to-beat heart rate data could be obtained until the last minute before birth. Because the ANOVA for

repeated measures automatically deletes observations with missing values, two separate analyses were performed, one for 20 fetuses until 9 minutes before birth and one for nine fetuses until the last minute before birth. Results of both analyses were comparable; therefore we present only *P*-values for the whole group of 20 fetuses.

Results

In total 20 fetuses were included, of which 10 had an umbilical artery pH < 7.05 (cases), and 10 had an arterial pH > 7.20 (controls). As shown in Table 5.1, fetuses with and without acidaemia were comparable with regard to gestational age ($P = 0.3$) and birthweight ($P = 0.3$). The neonatal 5-minute Apgar score was significantly lower in the acidaemia group compared with the control group ($P < 0.01$). Four fetuses with acidaemia and none of those without were admitted to the neonatal ward ($P = 0.09$). Five mothers in the case group and six mothers in the control group used epidural analgesia ($P = 0.65$). Seven women in the case group and three in the control group needed oxytocin augmentation ($P = 0.4$). According to the STAN® criteria, in the case group nine women had an abnormal and one had an intermediate CTG during the last 30 minutes of labour. In the control group eight women had an abnormal and two had an intermediate CTG ($P = 1.0$). During the last hour of labour, seven fetuses with acidaemia and four without had one or more ST-events ($P = 0.4$), of these, six and three, respectively, were significant ST-events indicating the need for intervention ($P = 0.4$). All ST-events were based on a rise in T/QRS ratio.

As shown in Figure 5.1, during the last 30 minutes of labour, there were no significant differences in absolute LF or HF spectral power of heart rate variability between fetuses with and fetuses without acidaemia, no significant differences within subjects over time and there was no significant interaction between acidaemic and non-acidaemic fetuses.

Table 5.1. Clinical characteristics of the included fetuses

	Fetuses with acidaemia (cases; *n* = 10)	**Fetuses without acidaemia (controls; *n* = 10)**
Gestational age (days)	283 (8)	278 (11)
Birthweight (grams)	3414 (423)	3643 (562)
5-minute Apgar score	8 (1)	10 (0)
Cord arterial pH	6.98 (0.07)	7.26 (0.03)
Cord venous pH	7.08 (0.1)	7.33 (0.04)
Cord arterial base excess (mmol/l)	-17 (4)	-5 (2)

Values are expressed as mean (standard deviation).

As shown in Figure 5.2, during the last 30 minutes before birth, LFn spectral power of heart rate variability was significantly higher in the acidaemia group and HFn spectral power of heart rate variability was significantly higher in the control group during the whole study period. We found no significant differences in LFn or HFn power within subjects over time and no significant interaction for these spectral values between fetuses with acidaemia and those without acidaemia.

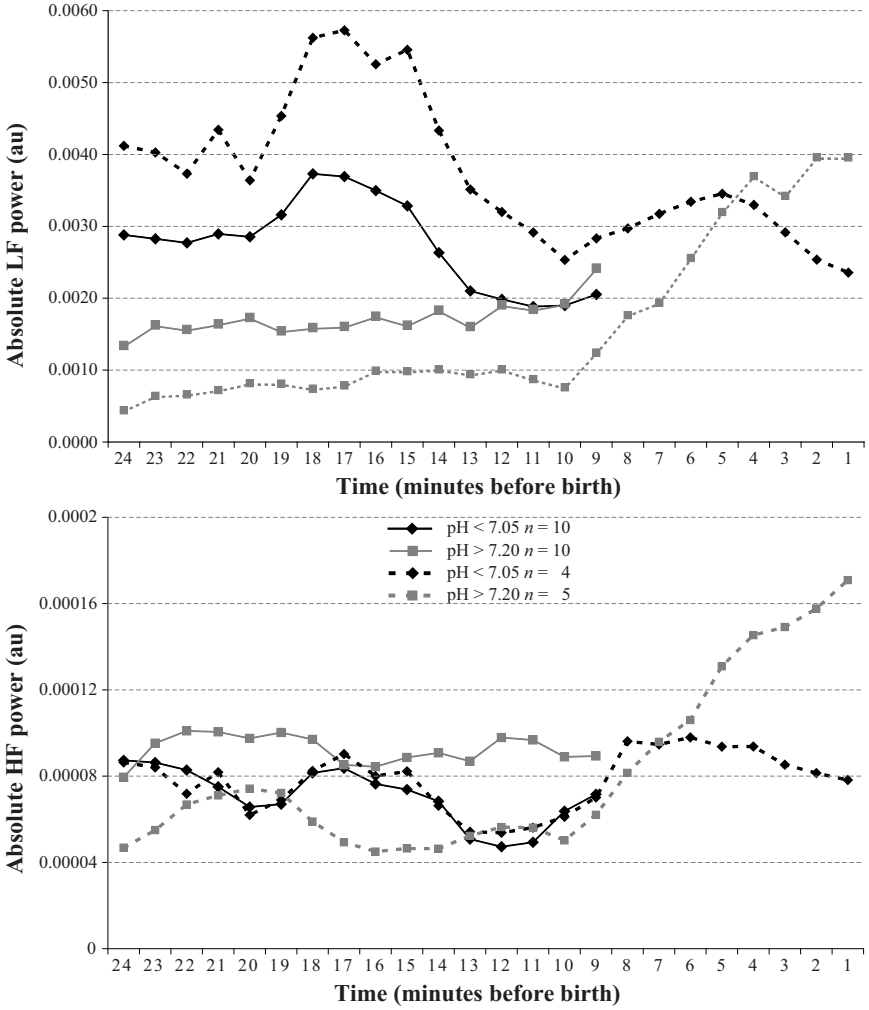


Figure 5.1. Absolute low frequency (LF) and high frequency (HF) spectral power of heart rate variability during the last minutes of labour in fetuses with acidaemia (pH < 7.05) and control fetuses without acidaemia (pH > 7.20). There were no differences in absolute LF or HF power between fetuses with acidaemia and those without (P = 0.2 and P = 0.3 respectively), no significant differences within subjects over time (P = 0.9 and P = 0.7 respectively) and no significant interaction was observed (P = 0.7 and P = 0.7 respectively). au, arbitrary units.

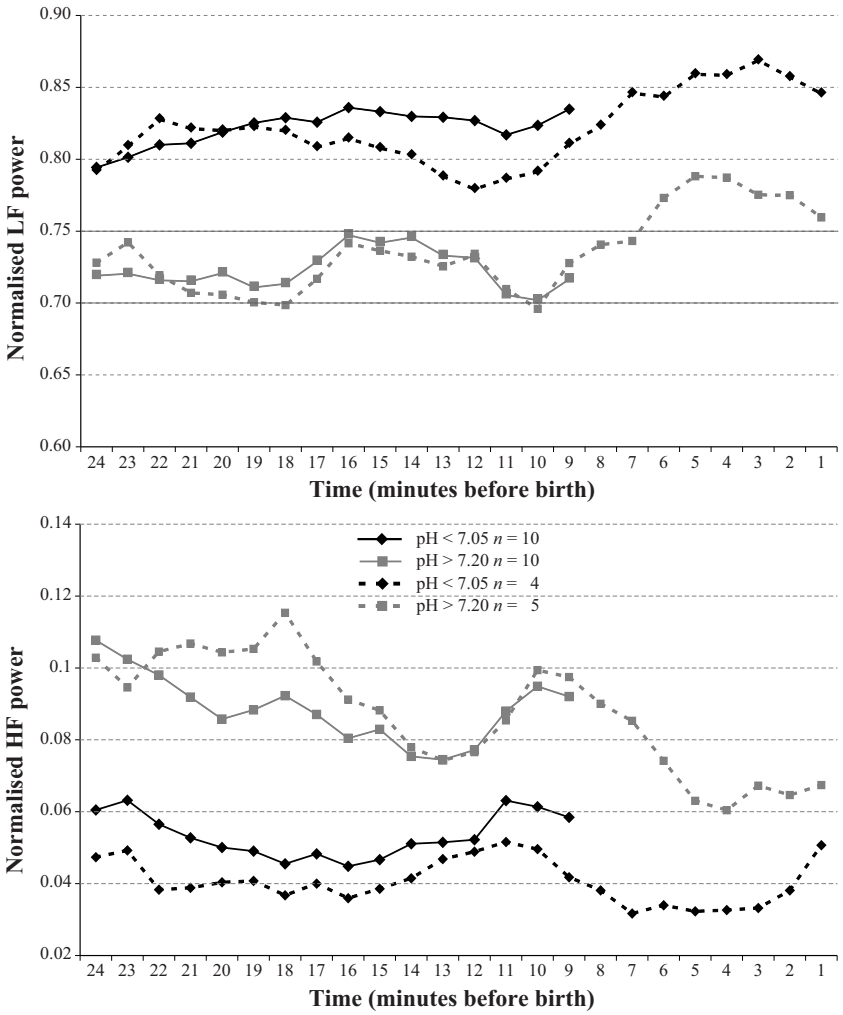


Figure 5.2. Normalised low frequency (LF) and high frequency (HF) spectral power of heart rate variability during the last minutes of labour in fetuses with acidaemia (pH < 7.05) and non-acidaemic control fetuses (pH > 7.20). Normalised LF power was significantly higher ($P = 0.01$) and normalised HF power was significantly lower ($P = 0.03$) in the acidaemia group. There were no differences within subjects over time ($P = 0.7$ and $P = 0.2$ respectively) and no significant interaction was observed ($P = 0.8$ and $P = 0.6$ respectively).

The observed significant differences in LFn and HFn power of heart rate variability between fetuses with and without acidaemia were not observed during the 1-hour period from 3 to 2 hours before birth (Figure 5.3).

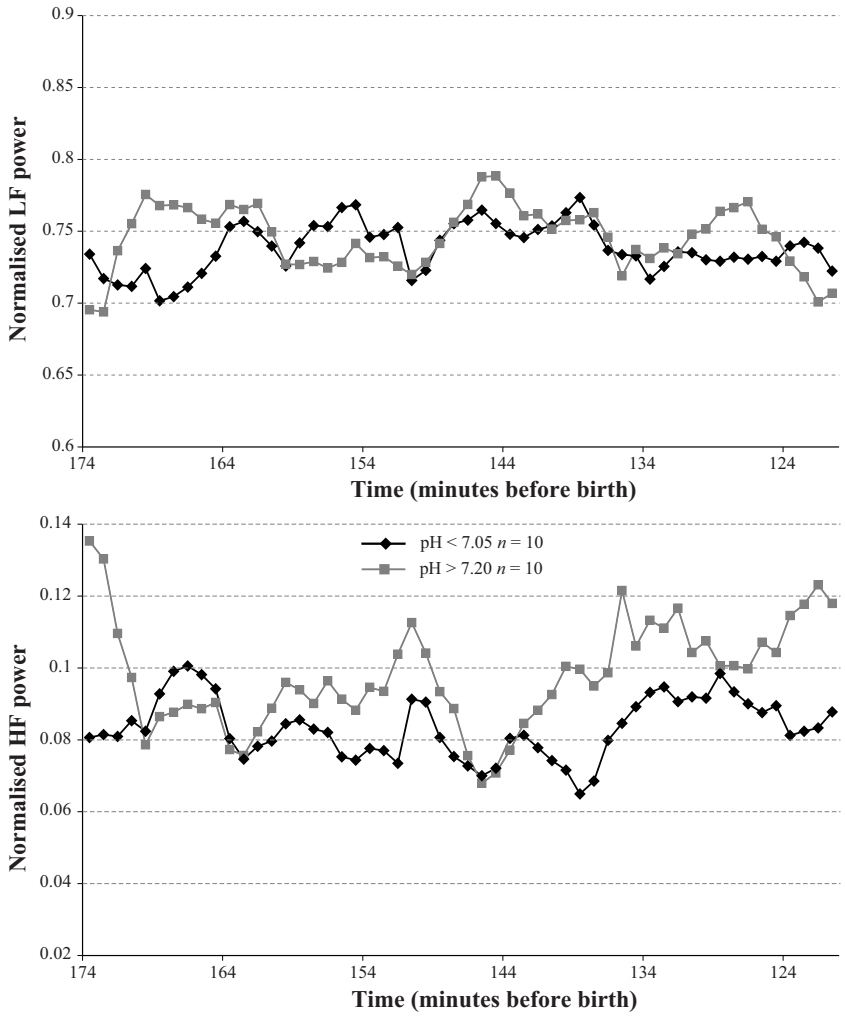


Figure 5.3. Normalised low frequency (LF) and high frequency (HF) spectral power of heart rate variability from 3 to 2 hours before birth in fetuses with acidaemia (pH < 7.05) and control fetuses without acidaemia (pH > 7.20). No differences in normalised LF or HF power between fetuses with and those without acidaemia were observed ($P = 0.7$ and $P = 0.9$ respectively).

Discussion

Spectral power of heart rate variability in the LFn band was significantly higher while spectral power of heart rate variability in the HFn band was significantly lower during the last 30 minutes of labour in the case of fetal acidaemia compared with fetuses in the non-acidaemic control group. In other words, slow oscillations in heart rate increase

while fast oscillations in heart rate decrease in case of fetal distress. This reflects a shift in autonomic modulation (sympathovagal balance) towards sympathetic predominance in fetuses with acidaemia. Spectral analysis objectively quantifies the variability in fetal heart rate as a function of frequency. Therefore, the observed differences in normalised spectral power between fetuses with and without acidaemia are the result of differences in fetal heart rate pattern. Despite this, CTG classification alone was not able to show differences between fetuses with acidaemia and those without. Therefore, it seems that spectral analysis is able to observe more subtle changes in fetal heart rate patterns that are difficult to observe in CTG.

Several studies have reported on normal values for the umbilical artery pH[18], pH values between 7.0 and 7.20 have been suggested as cut-off for fetal acidaemia[19]. We chose an umbilical artery pH of 7.05 as the cut-off value for severe fetal acidaemia, because this threshold is associated with major neurologic morbidity[19] and therefore, this cut-off is considered as clinically important. Furthermore, this value has been applied as a marker of severe fetal acidaemia in previous studies[2,10]. Because an umbilical cord arterial pH > 7.20 is considered normal after an uncomplicated vaginal delivery at term (> 10th percentile)[20] and as fetal acidaemia has traditionally been defined as an arterial pH < 7.20[21,22], the controls were defined as fetuses with an arterial pH > 7.20.

Previous studies using spectral analysis of fetal heart rate variability for fetal monitoring during labour used 2-minute continuous signal segments[10,14]. We used shorter signal segments of 64 seconds to produce power spectra, assuming that in such a short window the data have a greater likelihood of presenting a stable state. We chose a 64-second window because the longest cycle we were interested in is 0.04 Hz. It is required to have at least two repetitions of the longest cycle included and for computational efficiency the lowest power of two, exceeding two times this longest cycle, was chosen. Furthermore, because a moving, partly overlapping window was used for Fourier transformation, which was shifted every 0.25 seconds, the influence of non-stationarity was minimised.

In the absence of sudden catastrophic events, acidaemia in term fetuses is reported to develop in a period of at least 90 minutes[23]. Therefore, analysis was also performed for the 1-hour period from 3 to 2 hours before birth (i.e. before the second stage of labour). During this period a normal fetal pH is expected. Because the differences between fetuses with acidaemia and those without were not seen during this 1-hour period, it seems that the LFn and HFn response during the last 30 minutes of labour are acidaemia-associated alterations. Therefore, it is assumed that the increase in LFn power and the decrease in HFn power were the result of the stress of labour resulting in acidaemia instead of intrinsic differences in fetal autonomic modulation that already exist in an early stage of labour.

Fetal heart rate variability is positively related to gestational age and negatively associated with birthweight[10]. It is important to emphasise that none of the included fetuses was growth retarded and that gestational age and birthweight were comparable between the groups. Therefore, in our study the observed differences between fetuses with and

without acidaemia were not the result of differences in these fetal baseline characteristics. Furthermore, our results were not biased by maternal use of medication influencing fetal autonomic modulation. Epidural injection may cause minimal, transient changes in fetal heart rate[24]. Although a small and non-significant difference exists between fetuses with and without acidaemia in epidural use, these differences are unlikely to influence our results, because these epidural-induced changes in fetal heart rate resolve within 30 minutes[24].

Although accelerations and decelerations influence fetal heart rate variability, spectral analysis was performed on continuous signal segments, because ignoring accelerations and decelerations would lead to results with little physiologic relevance. Accelerations were not seen during the last 30 minutes of labour in any of the included registrations and the CTG classification according to the STAN® criteria during the last 30 minutes of monitoring was not different between the groups. Therefore, accelerations and decelerations per se are unlikely to account for the observed differences between fetuses with acidaemia and those without.

There is a strong correlation between a rise in T/QRS ratio and the level of circulating catecholamines[25] and hence anaerobic metabolism. Siira et al. found that an increase in T/QRS ratio is associated with an increase in LF heart rate variability[10]. In our study we found a non-significant trend toward increased rates of ST-events based on a rise in T/QRS ratio in fetal acidaemia.

Previous studies in human fetuses found a decrease in absolute LF and HF power during severe fetal compromise[10,11,12,13,14]. This was thought to represent a sign of decompensation of the fetal circulatory system[10]. In our study we could not confirm this fetal autonomic decompensation. On the contrary, we found that even in severe fetal metabolic acidaemia, although HFn power was low, LFn power was high until the last minute before birth. Possibly the observed differences are the result of using absolute values in previous studies. If spectral components are expressed in absolute units, the changes in total power influence LF and HF power, concealing the relative distribution of the energy[9]. Because we found significant differences between fetuses with and those without acidaemia using normalised spectral values, normalisation seems to be more suitable. Although the sample size is quite small, it is unlikely that the observed differences are the result of chance alone because they are fully in line with the autonomic response to stress in adults[26]. On the other hand, the lack of significant differences in absolute spectral values between fetuses with and those without acidaemia could be the result of the small number of fetuses examined in our study. However, because of the strict inclusion and exclusion criteria we were not able to include more cases. To determine the diagnostic value for identification of fetuses at risk for severe acidaemia our results have to be verified in larger prospective studies.

Another possible limitation of our study is that the accuracy with which the beat-to-beat RR-intervals are available is 2 milliseconds, because the STAN® device has a sampling rate of 500 Hz. This is inadequate for short term variability measurement in the time-domain

as described by Dawes, because this method requires an accuracy of 1 millisecond[27]. However, for short term recordings frequency-domain measures are preferred over time-domain measures, because more knowledge exists on the physiological interpretation[9]. The European Society of Cardiology and the North American Society of Pacing and Electrophysiology state that the optimal sampling range for frequency-domain measures (spectral analysis) is 250-500 Hz[9]. This is in line with previous studies, which showed that increasing the sampling rate over 500 Hz barely changed spectral power values[28]. For spectral analysis sampling rates over 500 Hz are only required in people with extremely low heart rate variability (e.g. after cardiac transplantation)[29], which is not the case for the included fetuses.

Low frequency and high frequency power increases during the second and third trimester of pregnancy[30]. The sympathetic nervous system is effective as early as mid-gestation, while the parasympathetic nervous system matures much later in pregnancy and begins to exert typical reflex responses at term and reaches adult levels only after birth[31]. Furthermore, the fetal cardiovascular response to neurotransmitters increases with gestational age because of maturation of the neuroeffector system and this increase in sensitivity continues after birth[31]. This maturation of the autonomic nervous system might affect the fetal haemodynamic responses to stress. However, the observed increase in LFn and the decrease in HFn power indicate a shift from sympathovagal balance towards sympathetic predominance and reduced vagal modulation in the human fetus as a response to the stress of labour. This reaction is comparable to the autonomic nervous system response to physical stress in human adults[26]. Therefore, despite its incomplete development, the autonomic nervous system in human fetuses at term is capable of exerting a strong response to severe stress.

It has been known for a long time that decreased fetal heart rate variability is associated with fetal distress[32]. Both autonomic withdrawal and a maximally stimulated sympathetic input can lead to diminished heart rate variability[26]. Yu et al. found during fetal hypoxaemia (without acidaemia) an increase in LF and HF power of heart rate variability[33]. β-Adrenoceptor blockade had no effect on the changes in the power spectrum induced by hypoxaemia, whereas fetal heart rate decreased[33]. Therefore, they stated that this sympathetic influence on the fetal heart during hypoxaemia must be predominantly the result of increased adrenomedullary secretion of catecholamines instead of cardiac sympathetic neural activity. Gardner et al. showed that acute hypoxia in fetuses with acidaemia is also associated with great concentrations of plasma catecholamines[34]. It is unlikely that these high levels of circulating catecholamines cause LF fluctuations in heart rate. We found an increase in LFn power in fetal acidaemia. Therefore, we suggest that a saturating high level of circulating catecholamines and sympathetic neural activity, might be the conceptual basis of decreased heart rate variability in severe fetal distress in human fetuses at term. It might be speculated that the high level of catecholamines sensitises the sympathetic nervous system, which results in a relative increase of low frequency heart rate variability.

Conclusions

Spectral analysis of fetal heart rate variability improves our understanding of the physiological response of the human fetus to hypoxaemia and can provide valuable insight into pathophysiological conditions. Our study indicates that normalised LF and HF power are promising markers for fetal distress and could probably be useful to improve fetal monitoring. To determine the diagnostic value for identification of fetuses at risk for severe acidaemia, prospective studies are needed.

References

1. Alfirevic Z, Devane D, Gyte GM. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. Cochrane Database Syst Rev 2006.
2. Neilson JP. Fetal electrocardiogram (ECG) for fetal monitoring during labour. Cochrane Database Syst Rev 2006.
3. Westerhuis ME, Kwee A, van Ginkel AA, Drogtrop AP, Gyselaers WJ, Visser GH. Limitations of ST analysis in clinical practice: three cases of intrapartum metabolic acidosis. BJOG 2007;114: 1194-1201.
4. Nielsen PV, Stigsby B, Nickelsen C, Nim J. Intra- and inter-observer variability in the assessment of intrapartum cardiotocograms. Acta Obstet Gynecol Scand 1987;66:421-424.
5. Kwee A, Dekkers AH, van Wijk HP, van der Hoorn-van den Beld CW, Visser GH. Occurrence of ST-changes recorded with the STAN S21-monitor during normal and abnormal fetal heart rate patterns during labour. Eur J Obstet Gynecol Reprod Biol 2007;135:28-34.
6. van Ravenswaaij-Arts CM, Kollee LA, Hopman JC, Stoelinga GB, van Geijn HP. Heart rate variability. Ann Intern Med 1993;118:436-447.
7. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213: 220-222.
8. Siira S, Ojala T, Ekholm E, Vahlberg T, Blad S, Rosen KG. Change in heart rate variability in relation to a significant ST-event associates with newborn metabolic acidosis. BJOG 2007;114:819-823.
9. Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-1065.
10. Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Valimaki IA, Rosen KG, Ekholm EM. Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. BJOG 2005;112:418-423.
11. Suzuki T, Kimura Y, Murotsuki J, Murakami T, Uehara S, Okamura K. Detection of a biorhythm of human fetal autonomic nervous activity by a power spectral analysis. Am J Obstet Gynecol 2001;185:1247-1252.
12. Chung DY, Sim YB, Park KT, Yi SH, Shin JC, Kim SP. Spectral analysis of fetal heart rate variability as a predictor of intrapartum fetal distress. Int J Gynaecol Obstet 2001;73:109-116.
13. Ohta T, Okamura K, Kimura Y, Suzuki T, Watanabe T, Yasui T, Yaegashi N, Yajima A. Alteration in the low-frequency domain in power spectral analysis of fetal heart beat fluctuations. Fetal Diagn Ther 1999;14:92-97.
14. Rantonen T, Ekholm E, Siira S, Metsala T, Leino R, Ekblad U, Valimaki I. Periodic spectral components of fetal heart rate variability reflect the changes in cord arterial base deficit values: a preliminary report. Early Hum Dev 2001;60:233-238.
15. Peters CH, ten Broeke ED, Andriessen P, Vermeulen B, Berendsen RC, Wijn PF, Oei SG. Beat-to-beat detection of fetal heart rate: Doppler ultrasound cardiotocography compared to direct ECG cardiotocography in time and frequency domain. Physiol Meas 2004;25:585-593.
16. de Beer NA, Andriessen P, Berendsen RC, Oei SG, Wijn PF, Bambang Oetomo S. Customized spectral band analysis compared with conventional Fourier analysis of heart rate variability in neonates. Physiol Meas 2004;25:1385-1395.

17. van Laar JO, Porath MM, Peters CH, Oei SG. Spectral analysis of fetal heart rate variability for fetal surveillance: review of the literature. Acta Obstet Gynecol Scand 2008;87:300-306.
18. Gregg AR, Weiner PD. Normal umbilical arterial and venous acid-base and blood gas values. Clin Obstet Gynecol 1993;36:24-32.
19. Goldaber KG, Gilstrap LC, Leveno KJ, Dax JS, McIntire DD. Pathological fetal acidemia. Obstet Gynecol 1991;78:1103-1107.
20. Dudenhausen JW, Luhr C, Dimer JS. Umbilical artery blood gases in healthy term newborn infants. Int J Gynaecol Obstet 1997;57:251-258.
21. van den Berg P, Schmidt S, Gesche J, Saling E. Fetal distress and the condition of the newborn using cardiotocography and fetal blood analysis during labour. Br J Obstet Gynaecol 1987;94:72-75.
22. Gilstrap LC, Hauth JC, Schiano S, Connor KD. Neonatal acidosis and method of delivery. Obstet Gynecol 1984;63:681-685.
23. Fleischer A, Schulman H, Jagani N, Mitchell J, Randolph G. The development of fetal acidosis in the presence of an abnormal fetal heart rate tracing. I. The average for gestational age fetus. Am J Obstet Gynecol 1982;144:55-60.
24. Palmer CM, Maciulla JE, Cork RC, Nogami WM, Gossler K, Alves D. The incidence of fetal heart rate changes after intrathecal fentanyl labour analgesia. Anesth Analg 1999;88:577-581.
25. Rosen KG, Dagbjartsson A, Hendriksson BA, Langercrantz H, Kjellmer I. The relationship between circulating catecholamines and ST waveform in the fetal lamb electrocardiogram during hypoxia. Am J Obstet Gynecol 1984;149:190-195.
26. Malik M, Camm AJ. Components of Heart Rate Variability — What They Really Mean and What We Really Measure. Am J Cardiol 1993;72:821-822.
27. Dawes GS. The fetal ECG: accuracy of measurements. Br J Obstet Gynaecol 1993;100 Suppl 9: 15-17.
28. de Jong W. Blood Pressure Variability in Neonates. With a special focus on signal acquisition and signal processing. PhD Thesis, Eindhoven University of Technology, Eindhoven, 2000.
29. Merri M, Farden DC, Mottley JG, Titlebaum EL. Sampling frequency of the electrocardiogram for the spectral analysis of heart rate variability. IEEE Trans Biomed Eng 1990;37:99-106.
30. van Leeuwen P, Geue D, Lange S, Hatzmann W, Gronemeyer D. Changes in the frequency power spectrum of fetal heart rate in the course of pregnancy. Prenat Diagn 2003;23:909-916.
31. Assali NS, Brinkman CR, Woods JR, Dandavino A, Nuwayhid B. Development of neurohumoral control of fetal, neonatal, and adult cardiovascular functions. Am J Obstet Gynecol 1977;129: 748-759.
32. Paul RH, Suidan AK, Yeh S, Schifrin BS, Hon EH. Clinical fetal monitoring. VII. The evaluation and significance of intrapartum baseline FHR variability. Am J Obstet Gynecol 1975;123:206-210.
33. Yu ZY, Lumbers ER, Gibson KJ, Stevens AD. Effects of hypoxaemia on foetal heart rate, variability and cardiac rhythm. Clin Exp Pharmacol Physiol 1998;25:577-584.
34. Gardner DS, Fletcher AJ, Bloomfield MR, Fowden AL, Giussani DA. Effects of prevailing hypoxaemia, acidaemia or hypoglycaemia upon the cardiovascular, endocrine and metabolic responses to acute hypoxaemia in the ovine fetus. J Physiol 2002;540:351-366.

Chapter 6

Normalized spectral power of fetal heart rate variability is associated with fetal scalp blood pH

J.O.E.H. van Laar, C.H.L. Peters, S. Houterman, P.F.F. Wijn, A. Kwee and S.G. Oei

Published: Early Human Development 2011;87:259-263

Abstract

Background: Spectral power of fetal heart rate variability is related to fetal condition. Previous studies found an increased normalized low frequency power in case of severe fetal acidosis.

Aims: To analyze whether absolute or normalized low or high frequency power of fetal heart rate variability is associated with fetal scalp blood pH.

Study design: Prospective cohort study, performed in an obstetric unit of a tertiary-care teaching hospital.

Subjects: Consecutive singleton term fetuses in cephalic presentation that underwent one or more scalp blood samples, monitored during labour using ST analysis of the fetal electrocardiogram. Ten-minute continuous beat-to-beat fetal heart rate segments, preceding the scalp blood measurement were used.

Outcome measures: Absolute and normalized spectral power in the low frequency band (0.04-0.15 Hz) and in the high frequency band (0.4-1.5 Hz).

Results: In total 39 fetal blood samples from 30 patients were studied. We found that normalized low frequency and normalized high frequency power of fetal heart rate variability are associated with fetal scalp blood pH. The estimated ß of normalized low frequency power was -0.37 (95% confidence interval -0.68 to -0.06) and the relative risk was 0.69 (95% confidence interval 0.51-0.94). The estimated ß of normalized high frequency power was 0.33 (95% confidence interval 0.01-0.65) and the relative risk was 1.39 (95% confidence interval 1.01-1.92).

Conclusions: Normalized low and normalized high frequency power of fetal heart rate variability are associated with fetal scalp blood pH.

Introduction

Obstetricians base their assessment of fetal condition on visual inspection of cardiotocogram (CTG) recordings. Although this simultaneous recording of fetal heart rate and uterine contractions provides useful information about fetal condition, its introduction has led to an overdiagnosis of fetal distress and a subsequent increase in unnecessary operative interventions[1].

Fetal scalp blood sampling (FBS) in addition to CTG surveillance is reported to reduce the number of unnecessary caesarean sections for presumed fetal distress[2]. FBS is a valid technique for determining fetal acid-base status during labour[3]. A good correlation exists between scalp blood pH taken shortly before delivery and newborn umbilical cord pH[4]. Despite this, there is no widespread use in obstetric units due to technical inconveniences and analytical difficulties[3]. It is an invasive procedure that has to be repeated when CTG abnormalities persist, with a reported overall incidence of complications of 6%, of which hemorrhage and infections are the major problems[2]. In a Cochrane meta-analysis it was reported that during labour combined use of CTG and automatic ST-waveform analysis of the fetal electrocardiogram (STAN®, Neoventa Medical, Moelndal, Sweden) reduces the rates of severe metabolic acidosis at birth and instrumental vaginal delivery for fetal distress[5]. However, recently it has been shown that STAN® reduces only the incidence of metabolic acidosis in blood and not in extracellular fluid, without affecting neonatal outcome or operative deliveries[6]. In addition, although STAN® is associated with fewer FBS during labour[5], STAN® cannot be used adequately without the availability of FBS analysis or fetal stimulation tests[7]. This is due to the limited reliability of STAN® analysis in clinical practice under certain conditions; e.g. during the 20-minute calibration period at the beginning of each registration, during periods of poor signal quality, and during prolonged periods of an abnormal CTG pattern without ST-events[8].

Fetal heart rate variability is reported to be the most important intrapartum fetal heart rate parameter to predict the development of acidemia[9]. Therefore additional information on fetal wellbeing might be obtained by using spectral analysis of fetal heart rate variability. Spectral power, in various frequency bands, of fetal heart rate variability is related to fetal condition[10]. In a previous study we found that an increased normalized low frequency power of fetal heart rate variability was associated with severe fetal acidemia[11]. However, for this study cases having an umbilical cord arterial pH < 7.05 immediately after birth, were compared with controls having an arterial pH > 7.20[11]. Although there were significant differences in spectral power between these extremes, we wondered whether spectral power of heart rate variability is associated with fetal acidosis at an earlier stage. Therefore, the aim was to investigate whether absolute or normalized low frequency (LF) or high frequency (HF) power is associated with fetal scalp blood pH during labour.

Methods

A prospective cohort study was performed. All mothers delivering at Máxima Medical Center, a tertiary-care teaching hospital in the Netherlands, between April 2006 and July 2008, who were at least 18 years old, carried a singleton pregnancy with a fetus in cephalic presentation and had a gestational age of at least 36 weeks, were asked to participate in the multicentre STAN® trial[6]. Mothers who gave their informed consent were randomized between CTG plus FBS and CTG plus ST analysis of the fetal electrocardiogram (STAN®) for fetal surveillance[6].

For the current study we only considered fetuses randomized for CTG plus STAN® and included only those fetuses that required FBS and from which the STAN® registration was available. Indications for FBS using STAN® were; 1. abnormal CTG pattern at the start of the STAN® registration, 2. intermediate CTG pattern at the start of the STAN® registration and doubt about the fetal condition (e.g. meconium stained amniotic fluid), 3. abnormal CTG pattern without ST-event for at least 60 minutes and 4. poor signal quality and an intermediate or abnormal CTG pattern.

Since intrauterine growth restricted fetuses have limited LF[12] and increased HF[13] reactivity of cardiac control, pregnancies complicated by intrauterine growth restriction (IUGR), defined as a neonatal birthweight of below the 10th percentile, were excluded from analysis. Likewise, fetuses with congenital anomalies that could influence fetal autonomic control were excluded from analysis. Birthweight percentiles were based on the Dutch perinatal registration reference curves, which are corrected for gestational age, maternal parity and fetal sex[14]. Only good-quality fetal ECG recordings, defined as an artifact correction percentage of at most 5% during the 10-minute continuous signal segment preceding the fetal scalp blood measurement were included[15].

Potential confounding variables considered were CTG classification, ST-events, significant ST-events, epidural analgesia, hypertensive disease of pregnancy, meconium stained amniotic fluid and medication use. CTG assessment was performed according to the STAN® clinical guidelines[7]. ST-events were determined significant according to the STAN® clinical guidelines[7]. Hypertensive disease of pregnancy included pregnancy induced hypertension and preeclampsia. Pregnancy induced hypertension was defined as a diastolic blood pressure > 90 or a systolic blood pressure > 140. Preeclampsia was defined as combined hypertension and proteinuria (> 0.3 g/24 h). Medication considered was: oxytocin, prostin, pethidine, promethazine, ritodrine, labetalol, methyldopa, amoxicillin-potassium clavulanate, acetaminophen and insulin.

A frequency-specific assessment of heart rate variability by power spectral analysis is a well-established means of characterizing autonomic cardiac control[16]. Our method has been described in more detail in previous studies[11,17,18]. Fetal ECG was recorded during delivery using a single-helix scalp electrode (Goldtrace™, Neoventa Medical, Moelndal, Sweden) and a maternal skin electrode. The scalp electrode was connected to a STAN S31® monitor (Neoventa Medical, Moelndal, Sweden). The STAN® machine detected R-

peak locations and measured and digitized RR-intervals (sampling rate 500 Hz). These beat-to-beat RR-interval data sets were stored on a PC hard disc and analyzed off-line.

To obtain equidistant data for spectral analysis, RR-intervals were resampled at 4 Hz. To prevent incorrect RR-intervals from dominating the spectrum, possible incorrectly determined RR-interval values were corrected. An RR-interval was considered to be incorrect if it exceeded the range of 0.2 to 1.3 seconds (46 to 300 bpm) or deviated more than 12% from preceding successive RR-intervals[15]. These incorrect RR-intervals were removed from the dataset and replaced by linear interpolation between the last preceding and the first succeeding correct RR-interval. Linear interpolation reduces the variability of the dataset, but this outweighs the error that is introduced by not correcting artifacts. To minimize the effect of artifact correction on the calculated spectral estimates, only signals with less than 5% artifact correction were included for analysis[15]. In addition, the direct current component was subtracted and the signal was multiplied with a Parzen window function to reduce spectral leakage before calculating the Fourier transform. Spectral analysis from the RR-intervals was performed by using a short time Fourier transform. A minimum window length for spectral analysis of 64 seconds was chosen to minimize the effect of non-stationarity[11]. To obtain spectral information of the pre-processed beat-to-beat RR-intervals, 256-point Fourier transforms were calculated for partly overlapping intervals of 64 seconds, which were shifted every 0.25 seconds[15]. Total spectral power of heart rate variability (0.04-1.5 Hz) and spectral power in the LF band (0.04-0.15 Hz) and in the HF band (0.4-1.5 Hz) were calculated. In addition, normalized LF and HF power was calculated by dividing LF and HF power respectively by total power.

For statistical analysis SPSS 12.0 (SPSS inc., Chicago, USA) was used. For the continuous 10-minute signal segment preceding FBS measurement, mean absolute LF and HF power and mean normalized LF and HF power of heart rate variability were calculated. Fetal scalp blood pH values were predicted from each of these mean spectral power values. A fraction of the women included in the cohort (n = 9; 30%) underwent more than one FBS measurement. This violates the statistical assumption of independence of measurements. To correct for this non-independence, the linear regression model was estimated using the method of Generalized Estimating Equations (GEE)[19]. GEE extends the generalized linear model to allow for analysis of repeated measurements. Relative risks estimated from linear regression models based on generalized estimating equations, can be interpreted similarly to those derived from a simple linear regression model. The independent association between known risk factors for fetal distress and fetal scalp blood pH was estimated using the GEE procedure. In addition, for the factors univariately associated with fetal scalp blood pH, a multivariate analysis was performed to correct for confounders. The corrected quasi likelihood under independence model criterion (QICC) can be used to choose between two sets of model terms, given a correlation structure[19]. The model that obtains the smaller QICC is better according to this criterion.

Since studies about spectral analysis for fetal monitoring are extremely rare and heterogeneous[10], we were not able to perform a sample size calculation.

Results

Of the 1458 patients recruited in our hospital for the multicenter STAN® trial[6], 727 were allocated to the CTG plus STAN® group. Of these patients 75 (10%) underwent one or more FBS measurements; of these, six registrations could not be analyzed because of missing STAN® data and six fetuses were excluded because of IUGR. One of the excluded growth retarded fetuses had a mild fetal hydrops of unknown origin and one had a trisomy 21. No other congenital anomalies occurred in the remaining 63 fetuses. The remaining 63 fetuses underwent in total 91 FBS. Of these 91 FBS, 26 were excluded because there was no 10-minute continuous STAN signal segment available prior to FBS, 26 were excluded for poor signal quality (more than 5% artifact correction).

In total, 39 FBS from 30 fetuses remained for analysis. For 21 fetuses only one FBS and for nine fetuses two FBS could be included. Altogether, 36 (92%) FBS were obtained during the first stage and three (8%) during the second stage of labour. Four (10%) FBS were performed for an abnormal CTG pattern at the start of the STAN® registration, eight (21%) for an intermediate CTG pattern at the start of the STAN® registration and doubt about the fetal condition, 21 (54%) for an abnormal CTG pattern for at least 60 minutes without ST-event and six (15%) were repeated measures after a previous FBS pH value between 7.20 and 7.25.

There were no missing data for the variables of interest. Table 6.1 provides the patients' baseline characteristics.

Table 6.1. Patients' characteristics (n = 30)

	Mean (standard deviation) or number (percentage)
Maternal age (years)	34 (5)
Gestational age (days)	285 (8)
Parity	Nulliparous 19 (63%) Multiparous 11 (37%)
Pregnancy complications	Gestational diabetes 1 (3%) Hypertensive disease of pregnancy* 5 (17%) Post term 3 (10%) Pre-existent hypertension 2 (7%)
Meconium stained amniotic fluid	10 (33%)
Birthweight (grams)	3585 (450)

**Hypertensive disease of pregnancy: pregnancy induced hypertension or preeclampsia.*

Out of the 39 FBS measurements included in the study, 18 (46%) showed an intermediate CTG pattern and 21 (54%) showed an abnormal CTG pattern during the 1-hour period prior to the FBS measurement. During this period 32 (82%) showed no ST-events, seven

Table 6.2. Medication use prior to FBS (n = 39)

	Number (percentage)
Prostin	9 (23%)
Oxytocin	26 (67%)
Pain relief	Pethidine and Promethazine 4 (10%) Epidural 30 (77%)
Tocolysis	Ritodrine 3 (8%)
Other medication	Methyldopa 1 (3%) Amoxicillin-Potassium Clavulanate 1 (3%) Labetalol 1 (3%) Insulin 2 (5%) Acetaminophen 1 (3%)

Table 6.3. Association between possible risk factors for fetal distress and fetal scalp blood pH

		Relative risk (95% confidence interval)	***P*-value**
Absolute LF power		1.00 (1.00-1.00)	0.7
Absolute HF power		1.00 (1.00-1.00)	0.4
Normalized LF power		0.69 (0.51-0.94)	0.02
Normalized HF power		1.39 (1.01-1.92)	0.04
CTG classification	Intermediate	1.00	
	Abnormal	0.95 (0.90-0.99)	0.04
Epidural analgesia	No	1.00	
	Yes	0.94 (0.87-1.01)	0.1
Hypertensive disease of pregnancy	No	1.00	
	Yes	0.95 (0.90-0.99)	0.04
Meconium stained amniotic fluid	No	1.00	
	Yes	1.04 (0.98-1.09)	0.2
Oxytocin	No	1.00	
	Yes	0.97 (0.91-1.03)	0.3
Prostin	No	1.00	
	Yes	1.05 (0.99-1.1)	0.1
ST-events	No	1.00	
	Yes	0.99 (0.91-1.07)	0.8
Significant ST-event	No	1.00	
	Yes	0.98 (0.89-1.09)	0.7

(18%) showed one or more ST-events; five (13%) a baseline T/QRS rise, one (3%) an episodic T/QRS rise and one (3%) a baseline and an episodic T/QRS rise and biphasic ST-events. Of those events, three (43%) indicated the need for intervention (significant ST-events). Mean FBS pH value was 7.25 with a standard deviation of 0.09. Mean non-artifact signal quality was 98% with a standard deviation of 1.7%. Medication use prior to FBS is expressed in Table 6.2.

Table 6.3 displays the individual association between known risk factors for fetal distress and fetal scalp blood pH.

Figures 6.1 and 6.2 display scatter plots to visualize the association between normalized LF and normalized HF power and fetal scalp blood pH value.

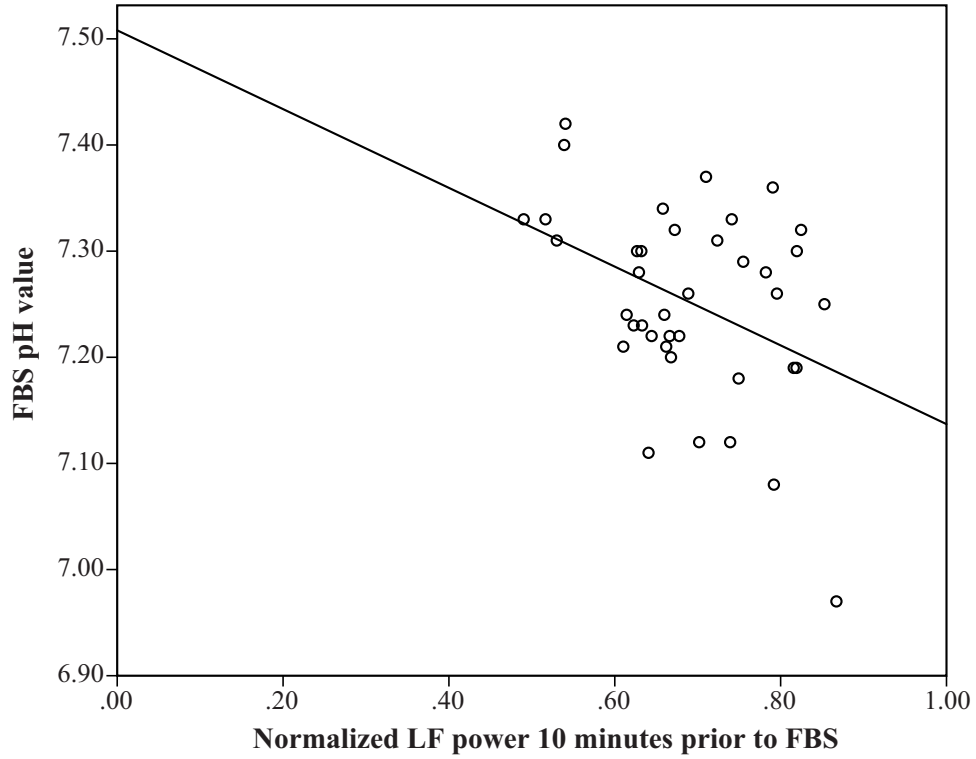


Figure 6.1. The association between normalized LF power and fetal scalp blood pH value. Reference line: Y = -0.37 * X + 7.51. FBS: fetal scalp blood sampling.

Normalized LF power of fetal heart rate variability was significantly associated with fetal scalp blood pH ($P = 0.02$). The intercept ß was 7.51 (95% confidence interval (CI) 7.31-7.71). The estimated ß of normalized LF power was -0.37 (95% CI -0.68 to -0.06) and the relative risk (RR) was 0.69 (95% confidence interval 0.51-0.94). The QICC was 4.27.

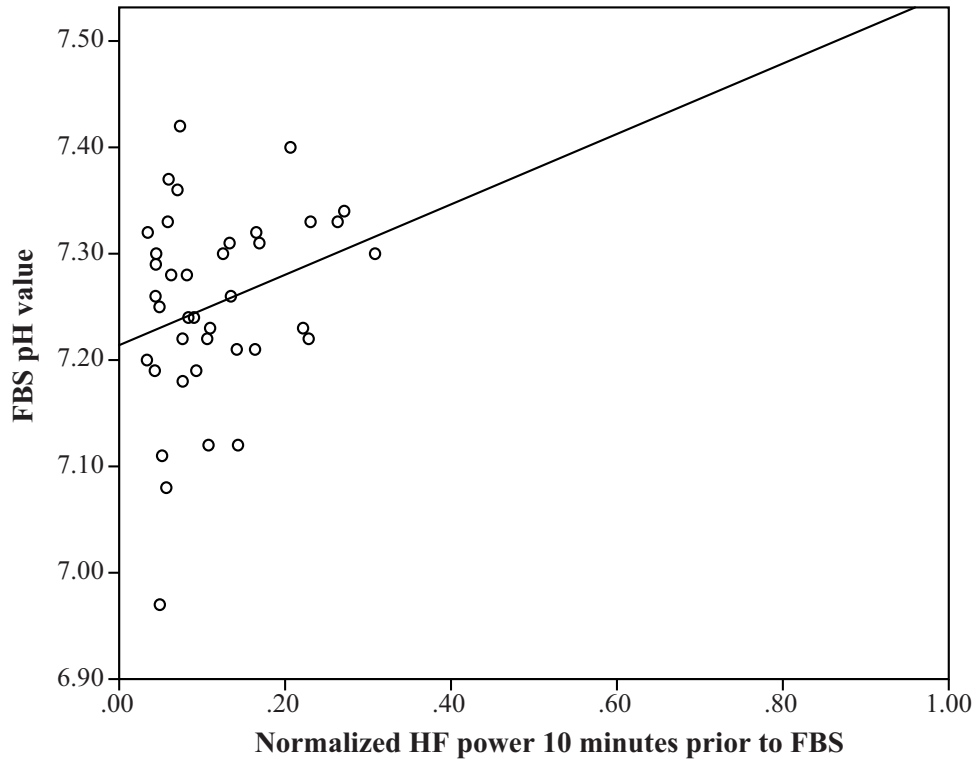


Figure 6.2. The association between normalized HF power and fetal scalp blood pH value. Reference line: Y = 0.33 * X + 7.21. FBS: fetal scalp blood sampling.

Normalized HF power of fetal heart rate variability was also significantly associated with fetal scalp blood pH ($P = 0.04$). The intercept ß was 7.21 (95% CI 7.16-7.27). The estimated ß of normalized HF power was 0.33 (95% CI 0.01-0.65) and the RR was 1.39 (95% confidence interval 1.01-1.92). The QICC was 4.29.

After adding CTG classification and hypertensive disease of pregnancy to the normalized LF power model, the RR of normalized LF power was 0.71 (95% CI 0.52-0.97; $P = 0.03$). The RR of an abnormal CTG pattern (compared to an intermediate CTG pattern) was 0.97 (95% CI 0.92-1.02; $P = 0.2$). The RR of hypertensive disease of pregnancy was 0.95 (95% CI 0.89-1.00; $P = 0.1$). The QICC was 8.24.

After adding CTG classification and hypertensive disease of pregnancy to the normalized HF power model, the RR of normalized HF power was 1.35 (95% CI 1.03-1.76; $P = 0.03$). The RR of CTG classification was 0.95 (95% CI 0.91-1.00; $P = 0.05$). The RR of hypertensive disease of pregnancy was 0.96 (95% CI 0.91-1.01; $P = 0.1$).The QICC was 8.26.

Discussion

LF and HF spectral power can be expressed as absolute or normalized units. In human adults normalization is recommended to make it possible to detect relative changes in LF or HF power[20], which could be masked by changes in total power. There are only a few studies published on spectral analysis of human fetal heart rate variability compared with umbilical cord blood-gas values[10]. In addition, studies are very heterogeneous in method of spectral analysis and frequency bands used[10]. Previous studies on human fetuses used absolute spectral values and found a decrease in absolute LF and HF power during severe fetal compromise[13,21,22,23,24]. We found that normalized LF and HF power of heart rate variability was significantly associated with fetal scalp blood pH value, while absolute LF and HF power was not. If spectral components are expressed in absolute units, the changes in total power influence LF and HF power in the same direction, concealing the relative distribution of the energy[20]. Because normalized values minimize the effect of changes in total power on the values of LF and HF power[20], normalized values seem more sensitive to detect fetal distress compared to absolute values. In a previous study we found that normalized LF power of heart rate variability was significantly higher and normalized HF power was significantly lower, during the last 30 minutes of labour, in fetuses with severe acidemia compared to healthy control fetuses[11]. In accord with this, the current study showed that normalized LF power was negatively associated and normalized HF power was positively associated with fetal pH. Since a good correlation exists between scalp blood pH taken shortly before delivery and newborn umbilical cord pH[4] it seems reasonable that this points to increased sympathetic and decreased parasympathetic cardiac modulation in human fetuses at term as their internal pH value decreases. This is in line with the previously observed increase in LF to HF ratio in acidotic fetuses, which reflects a shift towards sympathetic predominance[13]. The current study confirmed the hypothesis that normalized spectral values of fetal heart rate variability cannot only discriminate between severe fetal acidemia and normal fetal condition[11] but are also associated with fetal distress at an early stage. However, although our results are statistically significant, they are not yet clinically relevant given the broad confidence intervals due to the small numbers of included FBS. Since the indications for FBS during STAN® measurements are limited and since all FBS performed for poor signal quality (n = 26; 29%) and all FBS for an abnormal or intermediate CTG pattern obtained before or within 10 minutes from the start of the CTG registration had to be excluded (n = 26; 29%), only a minor part of the registrations was available for analysis (n = 39; 42%). Nevertheless, the included fetuses represent a heterogeneous group which reflects the clinical population and in spite of the limited clinical applicability at this stage our results are promising and fully in line with the physiological response to stress.

Meconium stained amniotic fluid, ST-events and significant ST-events were not individually associated with fetal scalp blood pH value (P = 0.2, P = 0.8 and P = 0.7 respectively). This is probably due to the research setting, since the presence of meconium stained amniotic fluid and the failure of ST-events to occur, indicate to perform FBS under certain conditions.

CTG classification was significantly associated with scalp blood pH value ($P = 0.04$). Since spectral analysis objectively quantifies the variability in fetal heart rate as a function of frequency, accelerations and decelerations influence spectral estimates of fetal heart rate variability. Despite this, spectral analysis was performed on continuous signal segments, because ignoring accelerations and decelerations would lead to results with little physiologic relevance. Hypertensive disease of pregnancy was also significantly associated with scalp blood pH value ($P = 0.04$) probably due to placental dysfunction. In previous studies women with preeclampsia and pregnancy induced hypertension are reported to experience atypical autonomic nervous system modulation of heart rate that is associated with a change in fetal heart rate pattern[25,26,27]. However, after adjusting for CTG classification and hypertensive disease of pregnancy, the association between normalized LF and normalized HF power respectively and fetal scalp blood pH remained. Therefore CTG classification and hypertensive disease were no confounding factors. Adding the variables CTG classification and hypertensive disease to the normalized LF and to the normalized HF model did not improve the models (QICC 8.24 and 8.26 respectively).

As expected we found a strong correlation between normalized LF and normalized HF power ($R = 0.7$). Therefore these parameters could not be merged into one model since that would violate the statistical assumption of no multicollinearity.

Medication use prior to or during FBS measurement could possibly affect our results. A univariate analysis was performed for oxytocin, prostin and epidural use. The numbers of patients included using other types of medication were too small to test a univariate correlation. Oxytocin, prostin and epidural analgesia were not associated with fetal scalp blood pH ($P = 0.3$, $P = 0.1$ and $P = 0.1$ respectively). Methyldopa was previously reported not to influence fetal heart rate variability[28] or fetal hemodynamics[29]. Therefore oxytocin, prostin, epidural and methyldopa are no confounding factors. Although the exact effect of amoxicillin-potassium clavulanate, acetaminophen and insulin on spectral estimates of fetal heart rate variability is unknown, based on physiological grounds no effect of these drugs on fetal cardiac autonomic response are expected. Four patients used pethidine and promethazine prior to FBS. Combined use of pethidine and promethazine is associated with a decrease in fetal heart rate variability[30]. Since patients used this medication 10 to 16 hours prior to FBS measurement, these drugs have probably not influenced our results. Ritodrine was used for tocolysis in case of presumed fetal distress prior to three FBS measurements. Ritodrine is reported to induce a decrease in heart rate variability[31]. In our study ritodrine was administered 5 minutes, 5 hours and 8 hours prior to FBS measurement. Because the half-life of ritodrine is short only one spectral power measurement might be influenced by ritodrine administration. One patient used labetalol for essential hypertension. Labetalol is also reported to decrease fetal heart rate variability[32,33]. Since the FBS 5 minutes after ritodrine admission was also the FBS during labetalol use, only one spectral estimate of heart rate variability could be biased by medication use. Excluding this FBS from analysis did not influence our results.

Our study has the limitation that the patients under study represent a heterogeneous group. This study design was chosen because a heterogeneous population resembles the clinical situation and increases generalizability. As stated above, the influence of baseline differences is small.

Recently the diagnostic test properties of STAN® combined with visual CTG interpretation during labour at term were questioned[6]. Probably, because the STAN® technology remains dependent on CTG interpretation, which lacks reproducibility and objectivity due to the high intra- and interobserver variation in the assessment of fetal heart rate patterns[34]. Spectral analysis of fetal heart rate variability is a non-invasive method which is able to investigate autonomic nervous system modulations and to provide objectively additional information on fetal condition. Normalized low and normalized high frequency power of fetal heart rate variability are significantly associated with fetal scalp blood pH value and might be able to detect fetal distress in an early stage. Therefore, this method could support CTG interpretation to achieve more objective CTG classification and might replace FBS analysis in addition to the STAN® technology in the future. However, first this must be confirmed by more extensive analysis.

References

1. Alfirevic Z, Devane D, Gyte GM. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. Cochrane Database Syst Rev 2006.
2. Young DC, Gray JH, Luther ER, Peddle LJ. Fetal scalp blood pH sampling: its value in an active obstetric unit. Am J Obstet Gynecol 1980;136:276-281.
3. Parer JT. The current role of intrapartum fetal blood sampling. Clin Obstet Gynecol 1980;23: 565-582.
4. Berg D, Saling E. The oxygen partial pressures in the human fetus during labor and delivery. In Longo LD, Bartels H (eds). Respiratory gas exchange and blood flow in the placenta. Department of health, education and welfare publications, Bethesda, USA 1972. Page 441-459.
5. Neilson JP. Fetal electrocardiogram (ECG) for fetal monitoring during labour. Cochrane Database Syst Rev 2006.
6. Westerhuis ME, Visser GH, Moons KG, van Beek E, Benders MJ, Bijvoet SM, van Dessel HJ, Drogtrop AP, van Geijn HP, Graziosi GC, Groenendaal F, van Lith JM, Nijhuis JG, Oei SG, Oosterbaan HP, Porath MM, Rijnders RJ, Schuitemaker NW, Sopacua LM, van der Tweel I, Wijnberger LD, Willekes C, Zuidhoff NP, Mol BW, Kwee A. Cardiotocography plus ST analysis of fetal electrocardiogram compared with cardiotocography only for intrapartum monitoring: a randomized controlled trial. Obstet Gynecol 2010;115:1173-1180.
7. Amer-Wahlin I, Arulkumaran S, Hagberg H, Marsal K, Visser GH. Fetal electrocardiogram: ST waveform analysis in intrapartum surveillance. BJOG 2007;114:1191-1193.
8. Westerhuis ME, Kwee A, van Ginkel AA, Drogtrop AP, Gyselaers WJ, Visser GH. Limitations of ST analysis in clinical practice: three cases of intrapartum metabolic acidosis. BJOG 2007;114: 1194-1201.
9. Williams KP, Galerneau F. Intrapartum fetal heart rate patterns in the prediction of neonatal acidemia. Am J Obstet Gynecol 2003;188:820-823.
10. van Laar JO, Porath MM, Peters CH, Oei SG. Spectral analysis of fetal heart rate variability for fetal surveillance: review of the literature. Acta Obstet Gynecol Scand 2008;87:300-306.
11. van Laar JO, Peters CH, Vullings R, Houterman S, Bergmans JW, Oei SG. Fetal autonomic response to severe acidemia during labour. BJOG 2010;117:429-437.
12. Breborowicz G, Moczko J, Gadzinowski J. Quantification of the fetal heart rate variability by spectral analysis in growth-retarded fetuses. Gynecol Obstet Invest 1988;25:186-191.
13. Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Valimaki IA, Rosen KG, Ekholm EM. Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. BJOG 2005;112:418-423.
14. Visser GH, Eilers PH, Elferink-Stinkens PM, Merkus HM, Wit JM. New Dutch reference curves for birthweight by gestational age. Early Hum Dev 2009;85:737-744.
15. Peters C, Vullings R, Bergmans J, Oei G, Wijn P. The effect of artifact correction on spectral estimates of heart rate variability. Conf Proc IEEE Eng Med Biol Soc 2008:2669-2672.
16. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213: 220-222.
17. Peters CH, ten Broeke ED, Andriessen P, Vermeulen B, Berendsen RC, Wijn PF, Oei SG. Beat-to-beat detection of fetal heart rate: Doppler ultrasound cardiotocography compared to direct ECG cardiotocography in time and frequency domain. Physiol Meas 2004;25:585-593.

18. de Beer NA, Andriessen P, Berendsen RC, Oei SG, Wijn PF, Bambang Oetomo S. Customized spectral band analysis compared with conventional Fourier analysis of heart rate variability in neonates. Physiol Meas 2004;25:1385-1395.
19. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13-22.
20. Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-1065.
21. Suzuki T, Kimura Y, Murotsuki J, Murakami T, Uehara S, Okamura K. Detection of a biorhythm of human fetal autonomic nervous activity by a power spectral analysis. Am J Obstet Gynecol 2001;185:1247-1252.
22. Chung DY, Sim YB, Park KT, Yi SH, Shin JC, Kim SP. Spectral analysis of fetal heart rate variability as a predictor of intrapartum fetal distress. Int J Gynaecol Obstet 2001;73:109-116.
23. Ohta T, Okamura K, Kimura Y, Suzuki T, Watanabe T, Yasui T, Yaegashi N, Yajima A. Alteration in the low-frequency domain in power spectral analysis of fetal heart beat fluctuations. Fetal Diagn Ther 1999;14:92-97.
24. Rantonen T, Ekholm E, Siira S, Metsala T, Leino R, Ekblad U, Valimaki I. Periodic spectral components of fetal heart rate variability reflect the changes in cord arterial base deficit values: a preliminary report. Early Hum Dev 2001;60:233-238.
25. Swansburg ML, Brown CA, Hains SM, Smith GN, Kisilevsky BS. Maternal cardiac autonomic function and fetal heart rate in preeclamptic compared to normotensive pregnancies. Can J Cardiovasc Nurs 2005;15:42-52.
26. Montan S, Ingemarsson I. Intrapartum fetal heart rate patterns in pregnancies complicated by hypertension. A cohort study. Am J Obstet Gynecol 1989;160:283-288.
27. Yum MK, Kim CR, Park EY, Kim JH. Instability and frequency-domain variability of heart rates in fetuses with or without growth restriction affected by severe preeclampsia. Physiol Meas 2004;25:1105-1113.
28. Wide-Swensson D, Montan S, Arulkumaran S, Ingemarsson I, Ratnam SS. Effect of methyldopa and isradipine on fetal heart rate pattern assessed by computerized cardiotocography in human pregnancy. Am J Obstet Gynecol 1993;169:1581-1585.
29. Montan S, Anandakumar C, Arulkumaran S, Ingemarsson I, Ratnam SS. Effects of methyldopa on uteroplacental and fetal hemodynamics in pregnancy induced hypertension. Am J Obstet Gynecol 1993;168:152-156.
30. Solt I, Ganadry S, Weiner Z. The effect of meperidine and promethazine on fetal heart rate indices during the active phase of labor. Isr Med Assoc J 2002;4:170-180.
31. Neri I, Monari F, Valensise H, Vasapollo B, Facchinetti F, Volpe A. Computerized evaluation of fetal heart rate during tocolytic treatment: comparison between atosiban and ritodrine. Am J Perinatol 2009;26:259-263.
32. Harper A, Murnaghan GA. Maternal and fetal haemodynamics in hypertensive pregnancies during maternal treatment with intravenous hydralazine or labetalol. Br J Obstet Gynaecol 1991;98: 453-459.
33. Montan S, Solum T, Sjoberg NO. Influence of the beta 1 adrenoceptor blocker atenolol on antenatal cardiotocography. Acta Obstet Gynecol Scand1984;118:99-102.
34. Nielsen PV, Stigsby B, Nickelsen C, Nim J. Intra- and inter-observer variability in the assessment of intrapartum cardiotocograms. Acta Obstet Gynecol Scand 1987;66:421-424.

Chapter 7

Power spectrum analysis of fetal heart rate variability at near term and post term gestation during active sleep and quiet sleep

J.O.E.H. van Laar, C.H.L. Peters, R. Vullings, S. Houterman and S.G. Oei

Published: Early Human Development 2009;85:795-798

Abstract

Background: Spectral analysis of fetal heart rate variability is promising for assessing fetal condition. Before using spectral analysis for fetal monitoring it has to be determined whether there should be a correction for gestational age or behavioural state.

Aims: Compare spectral values of heart rate variability between near term and post term fetuses during active and quiet sleep.

Study design: Case-control. Cases had a gestational age of ≥ 42 weeks; controls were 36 to 37 weeks. Fetuses were matched for birthweight percentile.

Subjects: STAN® registrations from healthy fetuses. For each fetus one 5-minute segment was selected during active and one during quiet sleep.

Outcome measures: Absolute and normalized low (0.04-0.15 Hz) and high frequency power (0.4-1.5 Hz) of heart rate variability.

Results: Twenty fetuses were included. No significant differences were found between cases and controls in absolute (481 and 429 respectively; $P = 0.88$) or normalized low (0.78 and 0.80 respectively; $P = 0.50$) or absolute (41 and 21 respectively; $P = 0.23$) or normalized high frequency power (0.08 and 0.07 respectively; $P = 0.20$) during active state. During rest, normalized low frequency power was lower (0.58 and 0.69 respectively; $P = 0.03$) and absolute (16 and 10 respectively; $P = 0.04$) and normalized high frequency power were higher (0.21 and 0.14 respectively; $P = 0.01$) in cases compared to controls. Absolute and normalized low frequency power were higher during active state compared to rest in both groups (all P-values < 0.05).

Conclusions: We found sympathetic predominance during active state in fetuses around term. Post term parasympathetic modulation during rest was increased compared to near term.

Introduction

The fetal heart rate (FHR) is modulated by the autonomic nervous system (ANS). Spectral analysis can be used to quantify periodic changes in FHR. Frequency bands have been identified that can be related to the autonomic nervous system function[1]. In human adults the low frequency (LF) component is influenced by a combined sympathetic and parasympathetic nervous system fluctuation, whereas the high frequency (HF) component is mainly a reflection of a parasympathetic nervous system fluctuation[2]. The ratio between LF and HF is a reflection of the sympathovagal balance in the control of heart rate[2]. By measuring these parameters, ANS modulations can be examined.

Recently it has been shown that spectral analysis could be a promising marker for detection of fetal distress[3]. If spectral analysis is applied to intrapartum ECG measurements (STAN®) of human fetuses with a gestational age of 36 weeks onwards, an increase in normalized LF power is seen in case of severe fetal acidosis. Previous studies showed that absolute LF and HF power increase as pregnancy progresses, which is attributed to fetal autonomic maturation[4,5]. Although the rate of increase in LF and HF power slowed substantially during the beginning of the third trimester[4], it has been shown that the parasympathetic nervous system begins to exert typical reflex responses only at term gestation and reaches adult levels after birth[6]. Furthermore, the fetal cardiovascular response to neurotransmitters increases with gestational age because of maturation of the neuroeffector system and this increase in sensitivity continues after birth[6]. Therefore, before using spectral analysis for fetal monitoring during labour at term, it has to be determined whether there should be corrected for gestational age.

In addition, in most studies employing spectral analysis of fetal heart rate variability, behavioural states have not been taken into account. From a gestational age of 36 weeks onwards fetal behavioural states are observed by analysis of patterns of heart rate, body movements and eye movements[7]. Fetal autonomic fluctuations, and thus spectral power in the LF and HF bands, are influenced by the behavioural state[8]. Since these states continue during labour[9], the understanding of these influences is necessary for the interpretation of spectral values during labour at term.

During quiet sleep (behavioural state 1F) FHR is stable with a small oscillation bandwidth, episodes of regular breathing movements may occur, fetal body movements are absent or may occur sporadically and eye movements are absent[7]. During active sleep (behavioural state 2F) FHR has a wider oscillation bandwidth and frequent accelerations occur, repeated gross fetal body movements and continuous rapid eye movements are present and episodes of irregular breathing may occur[7]. In healthy fetuses after 34 weeks the linkage between these variables is so strong that the different states can be determined reliably by visual identification of heart rate patterns alone[10]. At 36 weeks, healthy fetuses are present in fetal state 1F circa 20% of the time, increasing up to 40% of the time at 40 weeks. In about 50% of the time, healthy fetuses at term are present in state 2F[11]. Fetal behavioural state 3F and 4F appear relatively rare[11].

The first objective of this study is to compare the absolute and normalized LF and HF spectral power of heart rate variability during labour, in near term fetuses (36-37 weeks) with post term fetuses (≥ 42 weeks) to examine whether differences in spectral power exist between the boundaries of the term period, which should be taken into consideration for fetal monitoring. The second goal is to study the quiet and active sleep states separately in both groups to determine the influence of fetal behavioural state on spectral values during labour around term.

Methods

A matched case-control study was performed. Cases were fetuses with a gestational age of ≥ 42 weeks. Controls had a gestational age of 36 to 37 weeks. Fetal gestational age was based on either the known last menstrual period or a first trimester ultrasound measurement. Because heart rate variability is negatively related to fetal birthweight[12] fetuses were matched for fetal birthweight percentile. Birthweight percentiles were based on the Dutch perinatal registration reference curves, which are corrected for gestational age, maternal parity and fetal sex. Only good-quality STAN® registrations from healthy fetuses born with an umbilical artery pH > 7.20, from healthy mothers who experienced no complications during pregnancy or labour and did not use any medication except oxytocin or epidural analgesia were included. Each fetus had a neonatal birthweight of above the 25th percentile according to sex, maternal parity and gestational age. Pregnancies complicated by intrauterine growth restriction or fetal congenital anomalies were excluded.

The included registrations were made in our tertiary-care teaching hospital and were selected consecutively from the period April 2006 to January 2008. From these STAN® registrations two 5-minute 100% signal quality segments (free of ectopic beats and missing data) were selected from normal CTG patterns (normal baseline heart rate and no decelerations) during the first stage of labour. One segment was selected during a period of quiet sleep, defined as a FHR pattern A (stable heart rate with small oscillation bandwidth)[7], without accelerations and a FHR variance < 15 (bpm^2)[13]. One segment was selected during a period of active sleep, defined as a FHR pattern B (heart rate with a wide oscillation bandwidth between frequent accelerations)[7] and a FHR variance > 30 (bpm^2)[13]. One subtrace per activity state was taken from each subject. When multiple segments were available the segment with the lowest FHR variance was selected for the quiet sleep state and the segment with the highest FHR variance was selected for the active sleep state.

Data acquisition and signal processing

The fetal ECG was recorded during delivery using a single-helix scalp electrode (Goldtrace™) and a maternal skin electrode. The scalp electrode was connected to a STAN S31® monitor (Neoventa Medical, Moelndal, Sweden). Beat-to-beat RR-intervals were obtained from the selected fetal ECG registrations.

Spectral analysis

Spectral information about fetal beat-to-beat heart rate was obtained by using a short time Fourier transform. Data were resampled at 4 Hz and 256-point Fourier transforms were calculated for partly overlapping, intervals of 64 seconds, which were shifted every 0.25 seconds[14]. The direct current component was subtracted before calculating the Fourier transform and to reduce spectral leakage the signal was multiplied with a Parzen window function. Based on previous studies[3,15] as well as the physiological range of fetal heart and respiratory movement rate, the following frequency bands were chosen: total frequency band: 0.04 to 1.5 Hz, LF: 0.04 to 0.15 Hz and HF: 0.4 to 1.5 Hz. Absolute spectral power values were expressed in squared milliseconds. After calculating the spectral power of fetal heart rate variability in these frequency bands, normalized values were calculated by dividing LF and HF power by total power.

Statistical methods

From the selected 5-minute fetal beat-to-beat heart rate segments; mean heart rate variance, mean absolute and normalized LF power of heart rate variability, mean absolute and normalized HF power of heart rate variability and mean LF/HF were calculated. These parameters were compared between cases and controls during the active and the quiet sleep state. Because of the small number of included fetuses the Mann-Whitney test was used for intergroup comparison. For intragroup comparison of related samples the Wilcoxon Signed Ranks test was used. Significance was tested two-sided at an α level of 0.05.

Results

In total 20 STAN® registrations were selected (10 cases and 10 controls). Median gestational age was 42^{+0} (range 42^{+0} to 42^{+1}) weeks for the cases and 36^{+6} (range 36^{+0} to 37^{+0}) weeks for the controls. Both groups consisted of eight primiparous and two multiparous women. Median umbilical artery pH after birth was 7.26 (range 7.23-7.28) in the near term group and 7.25 (range 7.21-7.26) in the post term group.

In total 40 5-minute fetal beat-to-beat heart rate segments were analyzed (10 during active sleep and 10 during quiet sleep for both groups). As shown in Table 7.1, no significant differences were found in mean absolute LF power between cases and controls neither during the active state nor during the quiet state ($P = 0.88$ and $P = 0.45$ respectively). Mean absolute HF power was significantly higher in post term fetuses compared to their near term controls during quiet sleep ($P = 0.04$). During active sleep no significant differences in mean absolute HF power were observed between cases and controls ($P = 0.23$). For the normalized values; no differences were found between cases and controls in mean normalized LF power, mean normalized HF power or mean LF/HF during the active state ($P = 0.50$, $P = 0.20$ and $P = 0.15$ respectively). During quiet sleep mean normalized LF power and mean LF/HF were significantly lower ($P = 0.03$ and $P = 0.01$ respectively) and mean normalized HF power was significantly higher ($P = 0.01$) in post term compared to near term fetuses. No differences in fetal heart rate variance

were seen between cases and controls, neither during active sleep nor during quiet sleep ($P = 0.50$ and $P = 0.29$ respectively). Mean absolute LF and HF power were significantly higher during active compared to quiet sleep for both cases and controls (all P-values < 0.05). Mean normalized LF power and mean LF/HF were significantly higher and mean normalized HF power was significantly lower during the active state compared to the quiet state in both gestational age groups (all P-values 0.005).

Table 7.1. Spectral parameters for cases and controls during active and quiet sleep

Spectral parameter	36-37 GA $n = 10$		≥ 42 GA $n = 10$		P-value
LFa active	429.0	(410.1)	480.7	(347.7)	0.88
LFa quiet	92.0	(79.9)	55.6	(25.9)	0.45
HFa active	21.3	(7.3)	41.3	(36.0)	0.23
HFa quiet	10.5	(5.3)	16.4	(7.4)	0.04
LFn active	0.80	(0.08)	0.78	(0.06)	0.50
LFn quiet	0.69	(0.10)	0.58	(0.12)	0.03
HFn active	0.07	(0.03)	0.08	(0.03)	0.20
HFn quiet	0.14	(0.06)	0.21	(0.07)	0.01
LF/HF active	23.7	(13.5)	15.5	(5.7)	0.15
LF/HF quiet	8.6	(5.4)	3.6	(1.6)	0.01
Variance active	51.3	(21.9)	57.6	(22.9)	0.50
Variance quiet	5.8	(3.0)	6.3	(2.6)	0.29

Values are expressed as mean (standard deviation). For intergroup comparison a Mann-Whitney test was used. GA: gestational age (weeks), LFa: absolute low frequency power of heart rate variability, HFa: absolute high frequency power of heart rate variability, LFn: normalized low frequency power of heart rate variability, HFn: normalized high frequency power of heart rate variability, LF/HF: low to high frequency ratio.

Discussion

Our results show increased absolute LF and HF power of heart rate variability in both near term and post term fetuses during the active sleep state compared to quiet sleep. David et al., found in the LF range low FHR power spectrum values in the quiet compared to the active sleep state[5]. Karin et al. also presented significantly higher power during activity periods than during quiet states[13]. However, it is not surprising that these studies found an increase in absolute power values during the active state, since this state was defined by a visually observed increase in heart rate variability[5] or by an increase in heart rate variance[13], which are both associated with an increase in total power. The changes in total power influence LF and HF in the same direction and prevent the appreciation of the fractional distribution of the energy[2]. LF and HF in normalized units emphasize the

controlled and balanced behaviour of the two branches of the autonomic nervous system[2] and the effect of the changes in total power on the values of LF and HF components is minimized. In addition, since normalized spectral values seem more appropriate for fetal monitoring, we calculated normalized spectral values in addition to detect the relative differences in spectral values, and found an increased normalized LF power in both near term and post term fetuses during the active sleep state compared to quiet sleep. This is in accordance with healthy human adults, in whom the highest normalized value of the LF component was found during rapid eye movement (REM) sleep, while a minimal value of this spectral band was registered during non-rapid eye movement (non-REM) sleep[16].

We observed a decreased absolute LF and HF power during the quiet compared to the active sleep state, this seems to be attributable to decreased autonomic modulation in quiet sleep, in fetuses around term. Since we found an increased normalized HF and decreased normalized LF power in the quiet sleep compared to the active sleep state, there seems to be a greater decrease in sympathetic modulation than in parasympathetic modulation, which results in a relatively increased parasympathetic modulation in quiet sleep in fetuses around term. Our results are in line with the observed marked decline in sympathetic nerve activity during non-REM sleep in healthy human adults[17]. During active sleep absolute LF and HF power and normalized LF power increased while normalized HF power decreased. This indicates sympathetic predominance. The changes in the sympathovagal balance during the different sleep stages are also reflected by the LF/HF ratio, which was found to be higher during active sleep than during quiet sleep. This observed increase in sympathetic modulation reflected by an elevation of the absolute and normalized LF power during active sleep is fully in line with an increased activity registered directly from sympathetic fibers during REM sleep in healthy adults[17]. Our results are also similar to those obtained in healthy human adults, in whom non-REM sleep was associated with a relatively strong cardiac vagal influence, whereas during REM sleep sympathetic dominance in the autonomic balance was observed[18].

Previous research showed that premature and mature fetuses present significantly different power spectra of heart rate variability[13]. By measuring these parameters during pregnancy the development of the fetal ANS could be examined. Since the ANS reflects the central nervous system regulatory ability, investigating ANS activity during gestation might provide a tool for understanding fetal brain maturation[5]. We found that during quiescence the absolute and normalized HF power in the post term group increased significantly in relation to that in the near term group while normalized LF power and LF/HF in the post term group decreased significantly compared to the near term group. Although the absolute LF power during rest did not reach statistical significance, there was a strong trend towards decreased values as pregnancy progressed. Therefore, it seems that post term fetuses showed decreased sympathetic and increased parasympathetic modulation during rest, compared to their near term controls. This might suggest parasympathetic maturation in post term pregnancies. This is in line with Assali et al., who found a marked rise in the parasympathetic tone of the resting heart rate during the neonatal period and up until the adult state while the adrenergic tone became

considerably smaller[6]. Our results are similar to David et al. who displayed an increase in LF power of fetal heart rate variability during the end of the second and the beginning of the third trimester and found a LF power decrease at the end of the third trimester of pregnancy[5]. Van Leeuwen et al. observed that HF power of fetal heart rate variability increased more rapidly during pregnancy than the LF power[4]. They also found that LF/HF displayed a trend to lower values as pregnancy progressed[4]. An important limitation of these two developmental studies is that they neither classified fetal behavioural states nor used normalized spectral values for comparison between different gestational age groups. From the 36th week of gestation onwards the fetus spends approximately 90% of the time in active or quiet sleep[19]. In fetuses at term, heart rate variability is directly related to rest-activity patterns[20]. Therefore, it seems difficult to interpret spectral power values of heart rate variability, as behavioural states are not taken into consideration. Since fetal behavioural states continue during labour[9,21] we distinguished between quiet sleep and active sleep. In the healthy near term fetus a strong correlation exists between body and eye movements and the heart rate pattern[22]. As a result the heart rate pattern alone can reliably be used for state recognition in mature fetuses[10].

Growth retarded fetuses have limited LF reactivity of cardiac control[8]. During quiescence LF power is higher in growth retarded fetuses compared to normal fetuses while during active states the LF power increase as observed in healthy fetuses could not be observed in growth retarded fetuses[8]. Furthermore, HF power is negatively associated with fetal birthweight[12]. Therefore, we matched cases and controls based on their birthweight percentile and excluded growth retarded fetuses. Since fetal acidemia is associated with increased normalized LF power only fetuses with an umbilical artery pH > 7.20 at birth were included. Therefore, the observed differences between cases and controls were not due to differences in fetal baseline characteristics. In addition, due to the strict in- and exclusion criteria our results were not biased by maternal medication use or fetal congenital anomalies that could influence fetal autonomic cardiac control.

Fetal breathing movements are closely related to changes in fetal ANS activity and are reflected in the HF range of the power spectrum of heart rate variability[23]. In the human fetus at term a high frequency (0.7-0.9 Hz) peak in the range of fetal breathing movements is observed[23]. Therefore, it might be argued that the observed increase in normalized HF average power could be related to the increase in fetal breathing motion events and thus to the increased occurrence of respiratory sinus arrhythmia (RSA) at the end of the third trimester of pregnancy[24]. However, although fetal behavioural states continue during labour, fetal breathing activity is nearly abolished[20]. Since breathing movements in the normal fetus in labour are profoundly suppressed, the observed increase in absolute and normalized HF power in post term pregnancies during quiet sleep is not related to fetal breathing movements but seems to reflect developmental changes in parasympathetic modulation.

The onset of labour is associated with a marked change in fetal central nervous system state, mediated by a change in circulating prostaglandin levels[25]. This rise in prostaglandins results in reduced fetal breathing movements[26]. It was found that RSA did not invariably

disappear during periods of apnoea[27]. Therefore, in addition to a peripheral component, a central component may be involved in the genesis of RSA. These observations might imply that fetal breathing movements may be a result of a surge in ANS activity and not the other way around. Based on our observations, post term fetuses probably have a greater intrinsic resting cardiac parasympathetic tone due to autonomic development compared to near term fetuses.

Conclusions

We found that fetal behavioural state and gestational age cause a considerable variability in absolute and normalized low and high frequency spectral power of heart rate variability during labour in fetuses around term. Based on previous studies, one does expect the LF and HF power to be related to sympathetic and parasympathetic nervous system modulation. Spectral analysis may thus provide us with a potential tool for the detection of pathological processes within the ANS, for example fetal distress. However, the use of spectral analysis of fetal heart rate variability as a clinical tool requires large prospective studies. Our results point out that correction for gestational age and fetal behavioural state in fetuses around term is required.

References

1. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213: 220-222.
2. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-1065.
3. van Laar JO, Porath MM, Peters CH, Oei SG. Spectral analysis of fetal heart rate variability for fetal surveillance: review of the literature. Acta Obstet Gynecol Scand 2008;87:300-306.
4. van Leeuwen P, Geue D, Lange S, Hatzmann W, Gronemeyer D. Changes in the frequency power spectrum of fetal heart rate in the course of pregnancy. Prenat Diagn 2003;23:909-916.
5. David M, Hirsch M, Karin J, Toledo E, Akselrod S. An estimate of fetal autonomic state by time-frequency analysis of fetal heart rate variability. J Appl Physiol 2007;102:1057-1064.
6. Assali NS, Brinkman CR, Woods JR, Dandavino A, Nuwayhid B. Development of neurohumoral control of fetal, neonatal, and adult cardiovascular functions. Am J Obstet Gynecol 1977;129: 748-759.
7. Nijhuis JG, Prechtl HF, Martin CB, Bots RS. Are there behavioural states in the human fetus? Early Hum Dev 1982;6:177-195.
8. Breborowicz G, Moczko J, Gadzinowski J. Quantification of the fetal heart rate variability by spectral analysis in growth-retarded fetuses. Gynecol Obstet Invest 1988;25:186-191.
9. Spencer JA. Behavioral states and the peripartum period. Semin Perinatol 1992;16:217-222.
10. Pillai M, James D. The development of fetal heart rate patterns during normal pregnancy. Obstet Gynecol 1990;76:812-816.
11. Mulder EJ, Visser GH, Bekedam DJ, Prechtl HF. Emergence of behavioural states in fetuses of type-1-diabetic women. Early Hum Dev 1987;15:231-251.
12. Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Valimaki IA, Rosen KG, Ekholm EM. Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. BJOG 2005;112:418-423.
13. Karin J, Hirsch M, Akselrod S. An estimate of fetal autonomic state by spectral analysis of fetal heart rate fluctuations. Pediatr Res 1993;34:134-138.
14. Peters CH, ten Broeke ED, Andriessen P, Vermeulen B, Berendsen RC, Wijn PF, Oei SG. Beat-to-beat detection of fetal heart rate: Doppler ultrasound cardiotocography compared to direct ECG cardiotocography in time and frequency domain. Physiol Meas 2004;25:585-593.
15. de Beer NA, Andriessen P, Berendsen RC, Oei SG, Wijn PF, Bambang Oetomo S. Customized spectral band analysis compared with conventional Fourier analysis of heart rate variability in neonates. Physiol Meas 2004;25:1385-1395.
16. Busek P, Vankova J, Opavsky J, Salinger J, Nevsimalova S. Spectral analysis of the heart rate variability in sleep. Physiol Res 2005;54:369-376.
17. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 1993;328:303-307.
18. Vanoli E, Adamson PB, Lin B, Pinna GD, Lazzara R, Orr WC. Heart rate variability during specific sleep stages. A comparison of healthy subjects with patients after myocardial infarction. Circulation 1995;91:1918-1922.

19. Hirsch M, Karin J, Akselrod S. Heart rate variability in the fetus. In Malik M, Camm AJ (eds). Heart rate variability. Futura Publishing Company, New York, USA 1995. Page 517-531.
20. Richardson B, Natale R, Patrick, J. Human fetal breathing activity during electively induced labor at term. Am J Obstet Gynecol 1979;133:247-255.
21. Griffin RL, Caron FJ, van Geijn HP. Behavioral states in the human fetus during labor. Am J Obstet Gynecol 1985;152:823-833.
22. Mulder EJ, Boersma M, Meeuse M, van der Wal M, van de Weerd E, Visser GH. Patterns of breathing movements in the near-term human fetus; relationship to behavioural states. Early Hum Dev 1994;36:127-135.
23. Ferrazzi E, Pardi G, Setti PL, Rodolfi M, Civardi S, Cerutti S. Power spectral analysis of the heart rate of the human fetus at 26 and 36 weeks of gestation. Clin Phys Physiol Meas 1989;10:57-60.
24. Wakai RT. Assessment of fetal neurodevelopment via fetal magnetocardiography. Exp Neurol 2004;190:S65-S71.
25. Boylan P, Lewis PJ. Fetal breathing in labour. In Rolfe P (ed). Fetal and neonatal physiological measurements. Pitman Press, Bath, UK 1980. Page 256-261.
26. Murai DT, Wallen LD, Lee CC, Clyman RI, Mauray F, Kitterman JA. Effects of prostaglandins on fetal breathing do not involve peripheral chemoreceptors. J Appl Physiol 1987;62:271-277.
27. Groome LJ, Mooney DM, Bentz LS, Singh KP. Spectral analysis of heart rate variability during quiet sleep in normal human fetuses between 36 and 40 weeks of gestation. Early Hum Dev 1994;38:1-9.

Chapter 8

Beat-to-beat heart rate detection in multi-lead abdominal fetal ECG recordings

C.H.L. Peters, J.O.E.H. van Laar, R. Vullings, S.G. Oei and P.F.F. Wijn

Published: Medical Engineering & Physics 2012;34:333-338

Abstract

Reliable monitoring of fetal condition often requires more information than is provided by cardiotocography, the standard technique for fetal monitoring. Abdominal recording of the fetal electrocardiogram may offer valuable additional information, but unfortunately is troubled by poor signal-to-noise ratios during certain parts of pregnancy. To increase the usability of abdominal fetal ECG recordings, an algorithm was developed that enhances fetal QRS complexes in these recordings and thereby provides a promising method for detecting the beat-to-beat fetal heart rate in recordings with poor signal-to-noise ratios. The method was evaluated on generated recordings with controlled signal-to-noise ratios and on actual recordings that were performed in clinical practice and were annotated by two independent experts. The evaluation on the generated signals demonstrated excellent results (sensitivity of 0.98 for SNR $\geq$ 1.5). Only for SNR $<$ 2, the inaccuracy of the fetal heart rate detection exceeded 2 ms, which may still suffice for cardiotocography but is unacceptable for analysis of the beat-to-beat fetal heart rate variability. The sensitivity and positive predictive value of the method in actual recordings were reduced to approximately 90% for SNR $\leq$ 2.4, but were excellent for higher signal-to-noise ratios.

Introduction

Reliable monitoring of fetal condition remains one of the largest challenges in obstetrics nowadays. The information provided by cardiotocography, the standard technique for fetal monitoring, is limited and often additional information is required for accurate evaluation of fetal condition. Traditionally, this additional information is obtained from fetal blood sampling[1]. Unfortunately, fetal blood sampling only provides information on fetal condition at a single moment. Further disadvantages of fetal blood sampling are its invasiveness and the difficulty of the procedure. More recently, ST analysis of the fetal scalp electrocardiogram (ECG) has been introduced as addition to cardiotocography[2]. Although ST analysis provides information on a semi-continuous basis, the invasiveness of the method is still a disadvantage, as it can only be applied during labor and is not free of risks[3,4,5]. Apart from ST analysis, spectral analysis of fetal heart rate variability has also been shown to be a potential predictor for fetal condition[6,7]. Accurate spectral analysis of fetal heart rate variability requires a beat-to-beat measurement of the heart rate and this more or less has restricted the application of spectral analysis to fetal scalp ECG recordings. To overcome this restriction, the availability of a reliable method to record the fetal electrocardiogram non-invasively would be highly appreciated. This would allow for antepartum application of ECG waveform analysis and spectral analysis of fetal heart rate variability.

The fetal electrocardiogram can be measured non-invasively from the maternal abdomen during large parts of pregnancy and the measurement is completely safe for both mother and fetus. Ever since the first measurement of the fetal electrocardiogram by Cremer[8], it has remained a challenge to retrieve the fetal ECG from the mix of physiological signals and noise that is measured on the maternal abdomen. As the main interference is the maternal electrocardiogram, several techniques have been developed to remove the maternal electrocardiogram from the measurements, but with varying success[9,10,11]. In the 1970s clinical applications of the abdominal fetal electrocardiogram have been introduced, but these have disappeared with the growing success of Doppler ultrasound for antepartum cardiotocography. Recently, abdominal measurement of the fetal electrocardiogram has regained interest[12,13,14]. Due to the use of multi-lead recordings and advances in signal processing techniques, interference of the maternal electrocardiogram is no longer an issue, and the additional information that potentially can be obtained is of high clinical importance[15,16].

Despite all technological improvements, retrieving the fetal electrocardiogram remains a challenge as the amplitude of the measured fetal signal varies during pregnancy and also varies between patients. The various methods that have been developed to separate the fetal electrocardiogram from the measured signals all yield one or multiple channels that contain fetal ECG components. Due to the small amplitude of the fetal electrocardiogram, the signal-to-noise ratio (SNR) of the fetal ECG components in these channels is often relatively poor. Consequently, standard techniques for detecting QRS complexes fail to provide a reliable heart rate for these signals. Averaged heart rates can often be obtained[17], but provide less information and are not suitable for accurate

spectral analysis of heart rate variability. Evidently, a need exists for a method that can obtain the beat-to-beat fetal heart rate from fetal ECG recordings with poor signal-to-noise ratio. This need has initiated the development of an algorithm that incorporates a priori knowledge on the fetal electrocardiogram to detect the beat-to-beat heart rate. This work describes this algorithm and evaluates its performance on both generated signals with controlled signal-to-noise ratios and actual measurements that were performed in clinical practice.

Algorithm description

The algorithm is intended for detecting the beat-to-beat fetal heart rate from multi-lead electrophysiological recordings on the abdomen of a pregnant woman. The input of the algorithm consists of multiple channels of abdominal electrophysiological recordings from which the maternal electrocardiogram has been removed. The output that the algorithm provides, contains the recording times at which fetal QRS complexes have been detected.

Existing QRS detection methods

A wide variety of algorithms for detecting QRS complexes in ECG recordings have been proposed in literature. Most early algorithms have been based on processing of the first derivative of the electrocardiogram or on filtering. Of these algorithms, the Pan-Tompkins method[18] and its numerous variations[19,20] have found widespread use in real-time applications. With increasing computational power, more advanced methods for QRS detection have been introduced, including wavelets[21], neural networks[22], and several other approaches[23]. A review of these methods has demonstrated that the sensitivity and the specificity of the QRS detection are generally very high, but may be significantly affected by the presence of noise and artifacts[23]. To increase the robustness of the QRS detection in the presence of artifacts, multi-lead approaches have been introduced[24,25]. However, direct application of a multi-lead approach to abdominal recordings of the fetal ECG is prohibited by the large amount of noise that may be present in these recordings and the influence that the position of the fetus has on ECG lead orientation.

Fetal ECG enhancement

The strength of the fetal ECG components in multi-lead abdominal recordings depends among others on the position of the fetus and the electrical conduction towards the maternal abdominal skin, and varies strongly from channel to channel. Calculating linear combinations of these channels, generally improves the signal-to-noise ratio of the fetal ECG. In the fetal vectorcardiogram, of which the various channels are all different projections, the QRS complex is represented by a loop. Due to this loop, phase differences will exist between the fetal ECG components in different channels. These phase differences will widen the QRS complex when calculating linear combinations of different channels and therefore limit the improvement of the signal-to-noise ratio. In our approach, we correct for this phase difference before calculating the linear combinations. Linear combination of phase difference corrected signals will not only

reduce noise, but will also enhance the QRS complex, when compared to standard linear combination. The transformation of the multi-lead input signals $S_i(t)$ into new, non-physiological leads $V_j(t)$ is given by:

$$V_j(t) = \sum_i W_{j,i} \cdot S_i(t - \tau_i) \,. \tag{1}$$

Here, W is the j by i matrix with the weights for calculating the specific linear combinations and τ_i is the inter-channel phase difference calculated by cross-correlating a selected input signal $S_k(t)$ with each of the other input signals:

$$\tau_i = \arg\max_t \left| \sum_{t'} S_k^*(t') S_i(t + t') \right| . \tag{2}$$

Here, $S_k(t)$ is the channel that has the highest correlation with the average of all input channels.

In abdominal recordings, the orientation of the main electrical axis of the fetal heart is a priori unknown. To increase the chances that the calculated non-physiological leads contain significant fetal ECG components, we chose to calculate a set of four linear combinations that, for equal weights, correspond with 0°, 45°, 90° and 135°. This reduced set of four enhanced ECG leads is further processed to detect the beat-to-beat fetal heart rate. Figure 8.1 shows the calculated ECG leads (right) and the electrode configuration that was used for our measurements (left).

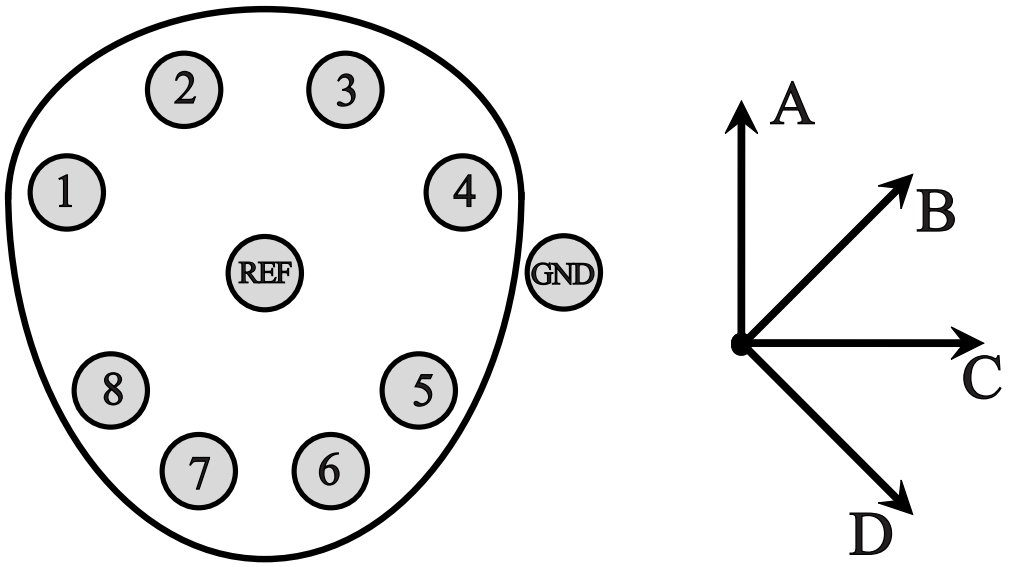


Figure 8.1. Used electrode configuration (left) and calculated ECG leads A, B, C, D for linear combinations with equal weights w_i (right).

The matrix *W* that transforms the multi-lead input signals measured with this electrode configuration into the ECG leads A, B, C and D is defined as:

$$W = \frac{1}{\sum w_i} \begin{pmatrix} w_1 & w_2 & w_3 & w_4 & -w_5 & -w_6 & -w_7 & -w_8 \\ 0 & 0 & \frac{2w_3}{a} & \frac{2w_4}{a} & 0 & 0 & \frac{-2w_7}{a} & \frac{-2w_8}{a} \\ -w_1 & -w_2 & w_3 & w_4 & w_5 & w_6 & -w_7 & -w_8 \\ \frac{-2w_1}{b} & \frac{-2w_2}{b} & 0 & 0 & \frac{2w_5}{b} & \frac{2w_6}{b} & 0 & 0 \end{pmatrix}, \quad (3)$$

with $a = \frac{\sum_{i=3,4,7,8} w_i}{\sum w_i}$ and $b = \frac{\sum_{i=1,2,5,6} w_i}{\sum w_i}$ and w_i the maximum value of the absolute cross-correlation that was calculated to determine the inter channel phase difference:

$$w_i = \max \left| \sum_{t'} S_k^*(t') S_i(t+t') \right|. \quad (4)$$

By enhancing the fetal ECG components in the recording, the signal-to-noise ratio of the resulting four leads significantly improves. Before processing these leads to detect the fetal heart rate, noise is further reduced by applying a band pass filter that matches the spectral content of the fetal QRS complexes (fourth order Butterworth filter, 12-42 Hz).

Fetal heart rate detection

To detect the beat-to-beat fetal heart rate from the calculated ECG leads, the absolute first derivatives of the four filtered signals $\widetilde{V}_j(t)$ are calculated and convoluted with a square function that matches the width of the fetal QRS complex. Then, the results are squared and summed over the four leads to provide the function $L(t)$:

$$L(t) = \sum_{j=1}^{4} \left(H(t) * \left| \frac{d\widetilde{V}_j(t)}{dt} \right| \right)^2, \quad (5)$$

with $H(t)$ a square function that was set to a width of 21 ms. To remove the DC-offset, $L(t)$ is high-pass filtered using a fourth order Butterworth filter with a cut-off frequency of 1 Hz. In the resulting signal, peaks are detected using a quadratic fit, which provides a first estimate of the times at which fetal QRS complexes are present in the recording. Based on these first estimates, the polarity of the QRS complexes in each of the four filtered ECG leads is determined and the four leads are combined to detect the exact location of the QRS complexes in the recording. Figure 8.2 illustrates the operation of the algorithm by showing the four enhanced fetal ECG leads after filtering $\widetilde{V}_1(t)$-$\widetilde{V}_4(t)$, as well as the calculated function $L(t)$ and the detected fetal QRS complexes.

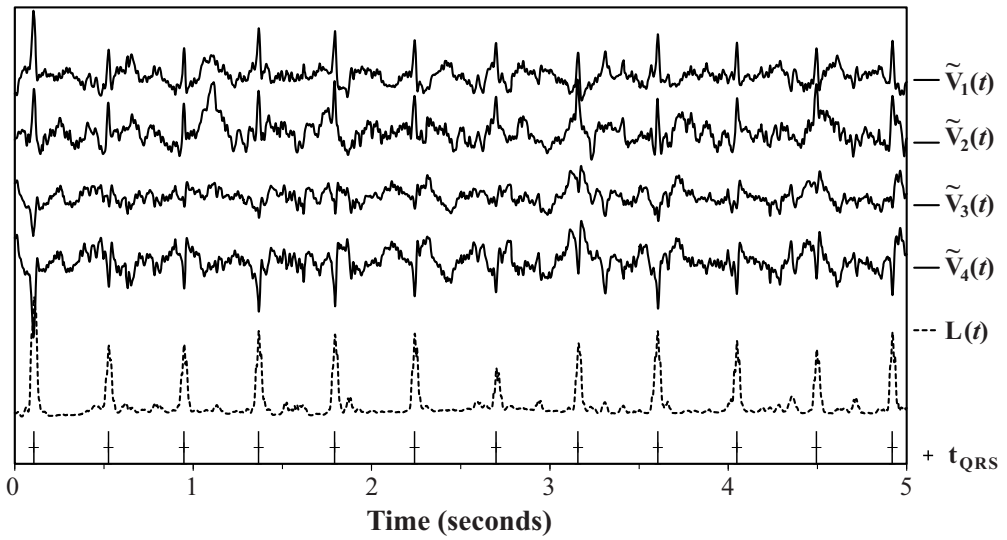


Figure 8.2. Illustration of the algorithm. The four upper curves are the calculated non-physiological leads $\widetilde{V}_1(t)$-$\widetilde{V}_4(t)$, the dashed line represents $L(t)$ calculated from $\widetilde{V}_1(t)$-$\widetilde{V}_4(t)$. The vertical lines at the bottom of the graph mark the actual times at which QRS complexes occur and the plus-signs mark the times at which QRS complexes have been detected by the algorithm.

Methods

The signal-to-noise ratio of abdominal fetal ECG recordings varies during pregnancy, between patients, and often also during the recording. Ideally, the performance of the algorithm is evaluated by determining the accuracy of QRS complex detection for various signal-to-noise ratios. Such an evaluation would require the availability of a golden standard to which the method can be validated. The golden standard for fetal heart rate detection is the fetal scalp ECG, which can only be applied during labor. However, at the end of pregnancy, when the fetal scalp ECG can be recorded, the signal-to-noise ratio of abdominal recordings is generally high. Therefore, direct comparison to the fetal scalp ECG will only provide information on the performance of the algorithm for recordings with relatively high SNR.

To evaluate the performance of the algorithm over a wider range of signal-to-noise ratios, a controlled amount of noise is added to generated signals. These generated signals with various signal-to-noise ratios, are analyzed by the algorithm and the results are compared to the actual QRS locations in the original noise-free signals. Additionally, actual clinical abdominal ECG recordings were analyzed and the results of the algorithm were evaluated visually by experts.

Generated recordings

Multi-lead electrocardiographic recordings were performed on the abdomen of a pregnant patient using a prototype non-invasive fetal ECG monitor (NEMO, Eindhoven University of Technology). The maternal ECG component in these recordings was estimated by means of a dynamic template subtraction technique[16]. The amplitude and timescale of the maternal ECG estimates were scaled to generate noise-free multi-lead signals that represent abdominally measured fetal ECG components. Next, actual measurement noise from abdominal recordings was amplified and added to the noise-free multi-lead signals, to provide artificial fetal ECG recordings at the desired signal-to-noise ratios. Signals were generated for signal-to-noise ratios of 10, 5, 4, 3, 2.5, 2, 1.5 and 1, where the SNR of the fetal ECG is defined as[17]:

$$SNR = \frac{\frac{1}{8}V_{pp,QRS}^2}{V_{rms,noise}^2}, \tag{6}$$

with $V_{pp,QRS}$ the mean peak-to-peak amplitude of the QRS complexes in the noise-free multi-lead signals and $V_{rms,noise}$ the rms amplitude of the noise that is added to the signals. The added measurement noise was different for each of the channels, but the signal-to-noise ratio was kept equal for all channels. Note that in actual abdominal fetal ECG measurements the signal-to-noise ratio will vary between channels. Figure 8.3 displays a generated multi-lead fetal ECG recording with a signal-to-noise ratio of 1. The performance of the algorithm was evaluated by comparing the times at which QRS complexes were detected in the generated signals, to the times at which QRS complexes were detected in the noise-free signals. For each signal-to-noise ratio, 360 seconds of multi-lead fetal ECG recording were generated and the generation and analysis of the signals was repeated up to 16 times.

Actual recordings

Abdominal fetal ECG recordings were performed on pregnant patients at the Máxima Medical Center in Veldhoven, the Netherlands using a prototype of a non-invasive fetal ECG monitor (NEMO, Eindhoven University of Technology). Measurements were performed during various stages of pregnancy. From these measurements, a selection of recordings with different signal-to-noise characteristics was processed by the algorithm. The detected fetal QRS complexes in a one-minute subset of each of these recordings were evaluated visually by two independent expert observers. A five-second segment of one of the analyzed recordings is displayed in Figure 8.4. The figure shows the eight measurement channels that each have a different signal-to-noise ratio. As the noise component in the recorded signal cannot easily be separated, $V_{rms,noise}^2$ in equation 6 cannot be measured directly. Instead, the total power of the recorded signal, V_{rms}^2, is measured. By modeling the QRS complex as one period of a cosine wave with duration T_{QS}, we may write (see Appendix):

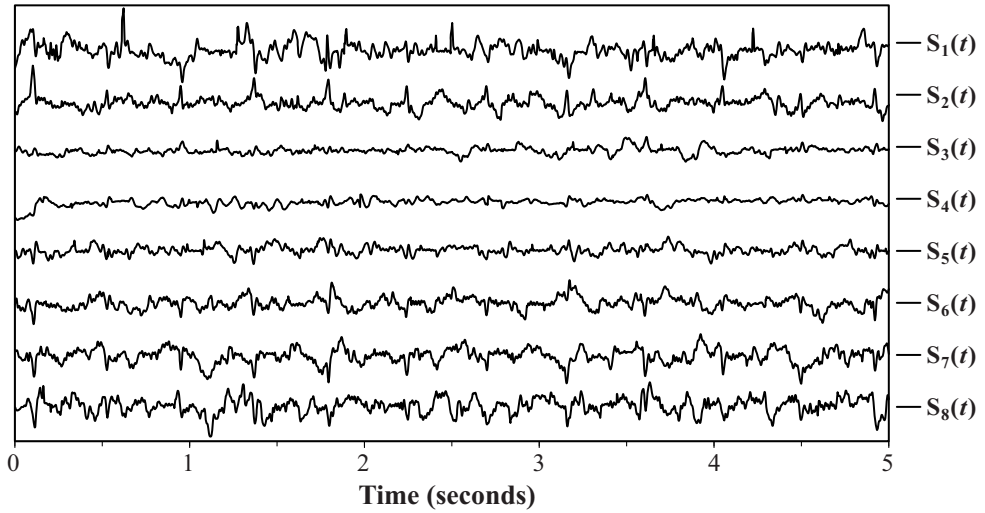


Figure 8.3. Five-second example of an eight channel generated fetal ECG recording with a signal-to-noise ratio of 1. This recording was used to illustrate the algorithm in Figure 8.2.

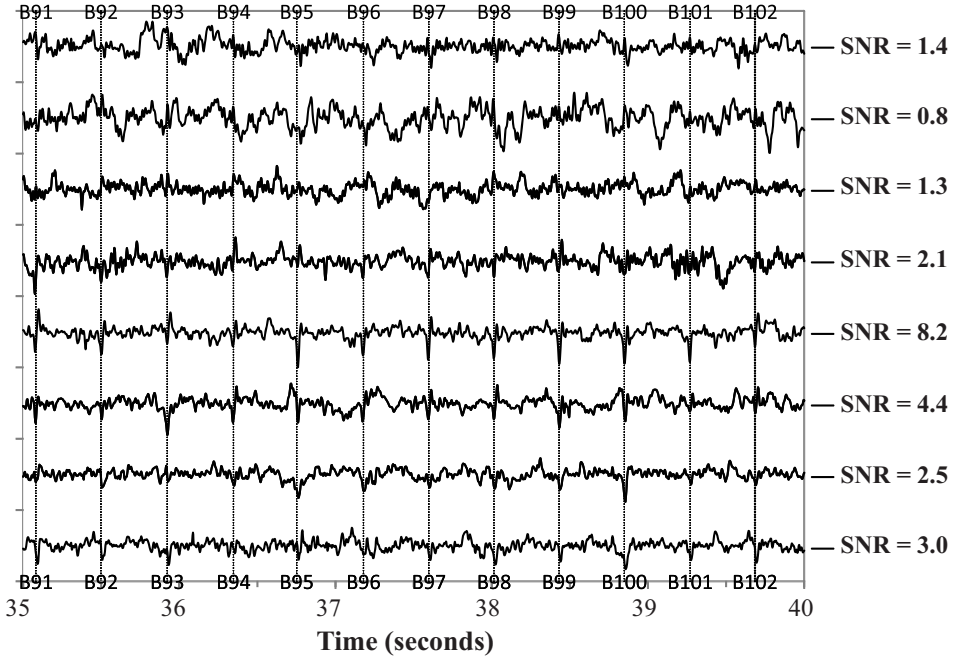


Figure 8.4. Five-second segment of an actual abdominal fetal ECG recording. The mean SNR of this segment is 3.0, but the SNR of the individual channels fluctuates between 0.8 (channel 2) and 8.2 (channel 5). The vertical dashed lines B91-B102 denote the detection of fetal QRS complexes by the developed method.

$$V_{rms}^2 \approx \left(2\frac{T_{QS}}{T_{RR}} + 1\right) V_{rms,noise}^2 \,, \tag{7}$$

with T_{QS} the duration of the fetal QRS complex, which typically is around 25 ms and T_{RR} the time between two consecutive QRS complexes. By using equations 6 and 7, the signal-to-noise ratio of each individual fetal ECG waveform can be calculated from the peak-to-peak amplitude of the QRS complex ($V_{pp,QRS}$), the total power of the recorded signal (V_{rms}^2) and the time between two consecutive QRS complexes (T_{RR}), which can all be determined from the recorded signals.

Results

Generated recordings

The noise-free signals that were used to generate the artificial abdominal fetal ECG recordings, contained 884 QRS complexes. The exact times at which QRS complexes were present in these signals were determined with an accuracy of 0.5 ms (i.e. 0.5•T_s, with T_s the sampling interval of the recording). These times were used to validate the times at which the algorithm detected QRS complexes in the generated abdominal fetal ECG recordings. The mean absolute error in the timing of the detected QRS complexes was calculated. Additionally, the number of missed QRS complexes was determined, as well as the number of extra, falsely detected, QRS complexes. Table 8.1 displays the results for each of the signal-to-noise ratios.

Table 8.1. Results of QRS detection for the generated abdominal fetal ECG recordings with various signal-to-noise ratios

SNR	Missed (%)	Extra (%)	Sensitivity	PPV	Error (ms)
10	2.1 ± 0.5	1.1 ± 0.3	0.98 ± 0.01	0.99 ± 0.00	0.08 ± 0.08
5	2.2 ± 0.6	1.1 ± 0.3	0.98 ± 0.01	0.99 ± 0.00	1.00 ± 0.07
4	2.1 ± 0.5	1.1 ± 0.4	0.98 ± 0.01	0.99 ± 0.00	1.04 ± 0.09
3	2.2 ± 0.6	1.2 ± 0.4	0.98 ± 0.01	0.99 ± 0.00	1.21 ± 0.10
2.5	2.1 ± 0.8	1.5 ± 0.5	0.98 ± 0.01	0.99 ± 0.01	1.23 ± 0.11
2	2.0 ± 0.6	1.8 ± 0.7	0.98 ± 0.01	0.98 ± 0.01	1.57 ± 0.51
1.5	2.4 ± 0.7	3.4 ± 1.9	0.98 ± 0.01	0.97 ± 0.02	2.32 ± 0.66
1	4.0 ± 1.0	12.7 ± 5.6	0.96 ± 0.01	0.89 ± 0.04	6.97 ± 3.70

Actual recordings

All QRS complexes that have been detected in the one-minute subsets of the actual recordings were evaluated visually. On average, these subsets contained 149 fetal QRS complexes. Extra, falsely detected, and missing QRS complexes were annotated in the recordings. These annotations were used to evaluate the performance of the algorithm,

similar to the evaluation for the generated recordings. The inaccuracy of the QRS detection expressed in the mean absolute error could not be determined as there was no information available on the exact times at which the QRS complexes are present in the recordings. Instead, it was annotated when the detection deviated slightly (< 10 ms) from the visually detected timing of the QRS complex. These detections were considered as falsely detected. Based on the correctly detected QRS complexes, the signal-to-noise ratio was estimated for each of the recordings. Table 8.2 shows the results for each of the recordings. The interobserver agreement was evaluated by comparing the annotations from both experts. Table 8.2 shows the overall proportion of agreement p_o and κ value for the recordings.

Table 8.2. Results of QRS detection for actual abdominal fetal ECG recordings with various signal-to-noise ratios

SNR	Missed (%)	Extra (%)	Sensitivity	PPV	p_o	κ
7.2	0	0	100	100	99.3	0.89
4.0	1.4	0	99.3	100	93.8	0.28
2.4	7.2	12.5	92.4	86.2	93.4	0.75
1.8	5.3	6.0	88.9	87.5	68.9	0.08
1.3	5.1	5.1	89.9	89.9	73.7	0.38

Discussion

Generated recordings

The results for the generated recordings show that even for relatively high signal-to-noise ratios, some QRS complexes remain undetected and also extra detections occur. The number of undetected QRS complexes remains relatively constant for signal-to-noise ratios of 1.5 and above and the sensitivity of the method is very high (0.98). For generated signals with SNR < 3, the number of extra detected QRS complexes slightly increases with decreasing signal-to-noise ratio. Consequently, the positive predictive value of the method decreases for lower signal-to-noise ratios. Additionally, the increased amount of noise in the generated recordings will affect the accuracy of the detection of fetal QRS complexes. For signal-to-noise ratios below 2, the inaccuracy of the QRS complex detection exceeds 2 ms, which may suffice for standard cardiotocography but is unacceptable for analysis of the beat-to-beat fetal heart rate variability[26].

Actual recordings

For the actual measurements with relatively high signal-to-noise ratios (mean SNR of 4 and 7.2), the numbers of undetected and extra detected QRS complexes are lower than for the generated recordings. However, this may be due to the relatively small number of QRS complexes in the subsets that were analyzed. For the actual measurements with low signal-to-noise ratios (mean SNR of 2.4 and lower), the numbers of undetected and

extra detected QRS complexes are by average 3.5 times higher than for the generated recordings with comparable signal-to-noise ratios. Consequently, both the sensitivity and the positive predictive value of the method are lower than for generated signals. Also, for the recordings with mean signal-to-noise ratios of 1.3 and 1.8 the interobserver agreement is rather poor κ values of 0.38 and 0.08). Due to their low signal-to-noise ratio, these recordings are difficult to interpret visually.

Interestingly, there is no evident relationship between the mean signal-to-noise ratio of the actual recordings on the one hand and the sensitivity and the positive predictive value of the method on the other hand. The observed fluctuation in sensitivity and positive predictive value of the method may result from the rather limited length of analysis. However, it is more likely that the mean signal-to-noise ratio of a recording does not characterize the quality of the signal sufficiently to quantify the performance of the method on actual recordings. As displayed in Figure 3, the signal-to-noise ratio strongly fluctuates over the channels of the recording. The mean signal-to-noise ratio of a recording therefore is not necessarily a good indicator for the performance of the method on that recording.

Conclusions

By incorporating a priori knowledge on the physiology of the fetal heart, the developed algorithm enhances fetal QRS complexes in multi-lead fetal ECG recordings. This provides a promising method for detecting the beat-to-beat fetal heart rate in recordings with poor signal-to-noise ratio. Evaluation of the method on generated fetal ECG signals with controlled signal-to-noise ratios showed excellent results for SNR $\geq$ 2. For signal-to-noise ratios below 2, the inaccuracy in the detection of the fetal QRS complex exceeds 2 ms, which prohibits analysis of the fetal heart rate variability in these signals. In actual recordings, the sensitivity and positive predictive value of the method are reduced to approximately 90% for SNR $\leq$ 2.4, but are excellent for higher signal-to-noise ratios.

Appendix

The total power in the recorded signal consists of the power P_{QRS} in the QRS complex and the power in the remaining signal, which is considered as noise P_{noise} :

$$P_{total} = V_{rms}^2 = P_{QRS} + P_{noise} \ . \tag{8}$$

The power of the noise in the recording is expressed as:

$$P_{noise} = V_{rms,noise}^2 = \frac{1}{8} V_{pp,noise}^2 \ , \tag{9}$$

with $V_{pp,noise}$ the peak-to-peak amplitude of the noise in the recorded signal.

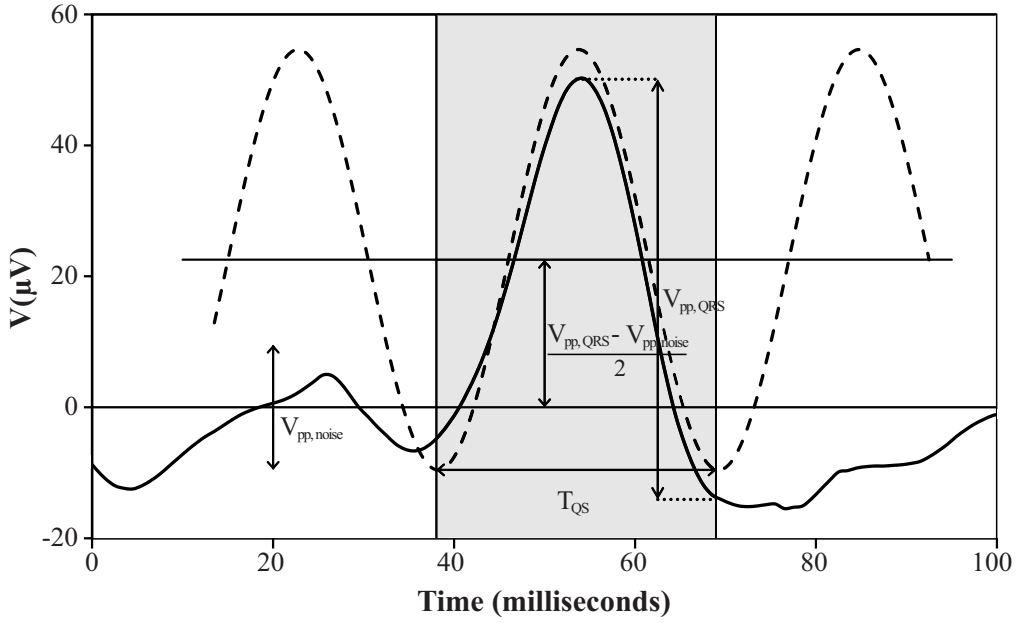


Figure 8.5. Modeling of the QRS complex of an ECG waveform by a cosine wave. The solid line represents a part of the ECG waveform, in which the grey area marks the QRS complex. The dashed line represents the cosine wave that is fitted to the QRS complex.

To estimate the power in the QRS complex, we model the QRS complex as one period of a cosine wave with duration T_{QS} at an offset of $\frac{V_{pp,QRS} - V_{pp,noise}}{2}$ with respect to the baseline of the recording:

$$\widetilde{V}_{QRS}(t) = \frac{V_{pp,QRS} - V_{pp,noise}}{2} - \frac{V_{pp,QRS}}{2} \cos\left(\frac{2\pi t}{T_{QS}}\right), \tag{10}$$

with T_{QS} the duration of the QRS complex. Figure 8.5 illustrates the modeling of the QRS complex. In the recording, fetal QRS complexes have a duration of T_{QS} and two consecutive complexes are separated T_{RR}. Using equation 10, the power of the QRS complexes in the signal can be expressed as:

$$\begin{aligned} P_{QRS} &= \frac{1}{T_{RR}} \int_0^{T_{QS}} \widetilde{V}_{QRS}^2(t)dt \\ &= \frac{T_{QS}}{T_{RR}} \left(\frac{V_{pp,QRS}^2}{8} + \left(\frac{V_{pp,QRS} - V_{pp,noise}}{2} \right)^2 \right), \end{aligned} \tag{11}$$

which by inserting equation 9 can be written as:

$$P_{QRS} = \frac{T_{QS}}{T_{RR}} \left(\frac{V_{pp,QRS}^2}{8} + \left(\frac{V_{pp,QRS} - \sqrt{8} V_{rms,noise}}{2} \right)^2 \right). \tag{12}$$

The total power P_{total} then becomes:

$$\begin{aligned} P_{total} = V_{rms}^2 &= \frac{T_{QS}}{T_{RR}} \left(\frac{V_{pp,QRS}^2}{8} + \left(\frac{V_{pp,QRS} - \sqrt{8} V_{rms,noise}}{2} \right)^2 \right) + V_{rms,noise}^2 \\ &= \left(2\frac{T_{QS}}{T_{RR}} + 1 \right) V_{rms,noise}^2 - \sqrt{2} \frac{T_{QS}}{T_{RR}} V_{pp,QRS} V_{rms,noise} + \frac{3}{8} \frac{T_{QS}}{T_{RR}} V_{pp,QRS}^2 . \end{aligned} \tag{13}$$

Under normal conditions, the latter two terms in equation 13 cancel out each other almost entirely. Consequently, we may write:

$$V_{rms}^2 \approx \left(2\frac{T_{QS}}{T_{RR}} + 1 \right) V_{rms,noise}^2 . \tag{14}$$

References

1. Beard RW. The detection of fetal asphyxia in labor. Pediatrics 1974;53:157-169.
2. Amer-Wåhlin I, Arulkumaran S, Hagberg H, K. Marsál K, Visser GH. Fetal electrocardiogram: ST waveform analysis in intrapartum surveillance. BJOG 2007;114:1191-1193.
3. Riskin A, Beni-Adani L, Chistiekov I, Kugelman A, Abend-Weinger M, Bader D. Cerebrospinal fluid leak in a premature neonate. Am J Perinatol 2005;22:57-59.
4. Miyashiro MJ, Mintz-Hittner HA. Penetrating ocular injury with a fetal scalp monitoring spiral electrode. Am J Ophthalmol 1999;128:526-528.
5. Eggink BH, Richardson CJ, Rowen JL. Gardnerella vaginalis-infected scalp hematoma associated with electronic fetal monitoring. Pediatr Infect Dis J 2004;23:276-278.
6. van Laar JO, Porath MM, Peters CH, Oei SG. Spectral analysis of fetal heart rate variability for fetal surveillance: review of the literature. Acta Obstet Gynecol Scand 2008;87:300-306.
7. van Laar JO, Peters CH, Vullings R, Houterman S, Bergmans JW, Oei SG. Fetal autonomic response to severe acidaemia during labour. BJOG 2010;117:429-437.
8. Cremer M. Über die direkte Ableitung der Aktionströme des menschlichen Herzens vom Oesophagus und über das Elektrokardiogramm des Fötus. Münch Med Wochenschr 1906;53:811-813.
9. Hon EH, Hess OW. Instrumentation of fetal electrocardiography. Science 1957;125:553-554.
10. Favret AG, Caputo AF. Application of computer techniques to the fetal electrocardiogram. Biomed Sci Instrum 1963;1:317-323.
11. Offner F, Moisand B. A coincidence technique for fetal electrocardiography. Am J Obstet Gynecol 1966;95:676-680.
12. de Lathauwer L, de Moor B, Vandewalle J. Fetal electrocardiogram extraction by blind source subspace separation. IEEE Trans Biomed Eng 2000;47:567-572.
13. Zarzoso V, Nandi AK. Noninvasive fetal electrocardiogram extraction: blind separation versus adaptive noise cancellation. IEEE Trans Biomed Eng 2001;48:12-18.
14. Ungureanu M, Bergmans JW, Oei SG, Strungaru R. Fetal ECG extraction during labor using an adaptive maternal beat subtraction technique. Biomed Tech (Berl) 2007;52:56-60.
15. Taylor MJ, Smith MJ, Thomas M, Green AR, Cheng F, Oseku-Afful S, Wee LY, Fisk NM, Gardiner HM. Non-invasive fetal electrocardiography in singleton and multiple pregnancies. BJOG 2003;110:668-678.
16. Vullings R, Peters CH, Sluijter RJ, Mischi M, Oei SG, Bergmans JW. Dynamic segmentation and linear prediction for maternal ECG removal in antenatal abdominal recordings. Physiol Meas 2009;30:291-307.
17. Peters CH, Vullings R, Bergmans JW, Oei SG, Wijn PF. Heart rate detection in low amplitude non-invasive fetal ECG recordings. Conf Proc IEEE Eng Med Biol Soc 2006;1:6092-6094.
18. Pan J, Tompkins WJ. A real-time QRS detection algorithm. IEEE Trans Biomed Eng 1985;32: 230-236.
19. Hamilton PS, Tompkins WJ. Quantitative investigation of QRS detection rules using the MIT/BIH arrhythmia database. IEEE Trans Biomed Eng 1986;33:1157-1165.
20. Arzeno NM, Deng ZD, Poon CS. Analysis of first-derivative based QRS detection algorithms. IEEE Trans Biomed Eng 2008;55:478-484.
21. Li C, Zheng C, Tai C. Detection of ECG characteristic points using wavelet transforms. IEEE Trans Biomed Eng 1995;42:21-28.

22. Xue Q, Hu YH, Tompkins WJ. Neural-network-based adaptive matched filtering for QRS detection. IEEE Trans Biomed Eng 1992;39:317-329.
23. Köhler BU, Henning C, Orglmeister R. The principles of software QRS detection. IEEE Eng Med Biol Mag 2002;21:42-57.
24. Moraes J, Freitas M, Vilani F, Costa E. A QRS detection algorithm using electrocardiogram leads. Comput Cardiol 2002;29:205-208.
25. Christov II. Real time electrocardiogram QRS detection using combined adaptive threshold. Biomed Eng Online 2004;3:28.
26. Dawes GS, Moulden M, Redman CW. System 8000: computerized antenatal FHR analysis. J Perinat Med 1991;19:47-51.

Chapter 9

Fetal heart rate variability in frequency-domain during pregnancy, obtained from non-invasive electrocardiogram recordings

J.O.E.H. van Laar, G.J.J. Warmerdam, R. Vullings, C.H.L. Peters, S. Houterman, P.F.F. Wijn, P. Andriessen, C. van Pul and S.G. Oei

Submitted for publication

Abstract

Objective: First, to study the relation between gestational age and spectral estimates of fetal heart rate variability, determined by non-invasive electrocardiogram. Second, to study the influence of fetal rest-activity state on spectral estimates.

Design: Prospective longitudinal study.

Setting: Tertiary-care teaching hospital.

Population: 35 healthy women, with an uneventful pregnancy.

Methods: A new method was developed to measure the fetal electrocardiogram non-invasively. Measurements were performed at regular time intervals (2 to 4 weeks) from a gestational age of 14 up to 41 weeks. Simultaneous ultrasound measurements were performed to assess fetal rest-activity state. From the fetal electrocardiogram measurements beat-to-beat heart rate was obtained for spectral analysis. 64-second segments of fetal heart rate were selected. Absolute and normalised power in the low (0.04-0.15 Hz) and high frequency band (0.4-1.5 Hz) were obtained, using a Fourier transform. Median values of spectral estimates, of the available segments from each measurement, were calculated. Data were analysed using linear regression for the periods below and above 30 weeks separately. For comparison between active and quiet state an independent *t* test was used.

Main outcome measures: First, spectral estimates as a function of gestational age. Second, spectral values during the active and the quiet state.

Results: The percentage of successfully retrieved heart rate data depend on gestational age. Before 18 and between 30 and 34 weeks no segments could be retrieved. During 21 to 30 weeks a significant increase in absolute low and high frequency power was observed, while no change in normalised spectral estimates was observed. During 34 to 41 weeks a (non-significant) decrease in absolute and normalised low frequency power and a (non-significant) increase in absolute and normalised high frequency power were observed. During the active state (near) term, absolute and normalised low frequency power were significantly higher and normalised high frequency power was significantly lower compared to the quiet state.

Conclusions: The observed increase in absolute spectral estimates, in preterm fetuses, was probably due to increased sympathetic and parasympathetic modulation and might be a sign of autonomic development. The observed non-significant changes in spectral estimates in (near) term fetuses might be associated with changes in behavioural state and increased parasympathetic modulation. However, more research is needed to confirm this. We found sympathetic predominance during the active state in (near) term fetuses.

Introduction

Cardiotocography is the widespread method for fetal monitoring despite its poor diagnostic value to detect fetal distress[1]. Poor specificity of this method has resulted in increased rates of operative deliveries without a significant improvement of long term fetal outcome[1]. Additional ST-waveform analysis of the fetal electrocardiogram (ECG; STAN®, Neoventa Medical, Moelndal, Sweden) and fetal scalp blood sampling (FBS), applied in case of a non-reassuring CTG, have limited capability to improve neonatal outcome or to reduce unnecessary interventions[1,2,3,4]. Besides, these techniques can only be used during labour at term due to their invasiveness. Therefore, an urgent need exists to develop non-invasive methods that provide complementary information on fetal wellbeing and enable intra- and antepartum use during the term and preterm period.

The analysis of variations in beat-to-beat heart rate is an established non-invasive technique for investigating the autonomic cardiac control system[5]. In human adults, heart rate variability (HRV) estimated by spectral analysis reflects the modulation of the sympathetic and parasympathetic limbs of the autonomic nervous system[5]. The low frequency (LF) cardiovascular fluctuations are ascribed to the baroreceptor reflex and are under sympathetic and parasympathetic control, whereas high frequency (HF) fluctuations are associated with respiration and are under parasympathetic control only[5,6].

As in human adults, quantifying the variations in beat-to-beat fetal heart rate by spectral analysis can be used to monitor autonomic nervous system modulation and may provide an early diagnostic tool for detection of fetal distress[7]. Spectral analysis during labour was previously performed on beat-to-beat heart rate, obtained from direct fetal ECG recordings by scalp electrode[7,8,9,10]. Our previous studies during labour showed that spectral estimates are associated with severe metabolic acidosis at birth[8] and might predict fetal distress in an early stage[9]. In addition, spectral estimates are related to fetal behavioural state and gestational age (GA) during labour at term[10].

Before using spectral analysis for fetal monitoring, more insight needs to be gained into normal autonomic development. However, at present, limited research has been done on human fetal HRV in frequency-domain, during the second and third trimester of pregnancy, and thus during the development of autonomic reflex mechanisms[11,12,13]. In order to measure spectral estimates during gestation, beat-to-beat fetal heart rate should be obtained non-invasively. Van Leeuwen et al. used magnetocardiography to measure fetal beat-to-beat heart rate[11]. Although this method produces a high quality fetal cardiac signal, it cannot be used in clinical practice due to the need of heavy magnetically shielded rooms. David et al. and Karin et al., measured beat-to-beat heart rate non-invasively from fetal ECG recordings[12,13]. However, both studies are limited considering developmental aspects, since no longitudinal follow up was performed during pregnancy. The three aforementioned studies reported conflicting results concerning changes in spectral estimates during the course of pregnancy. Two studies found an increase in LF and HF spectral estimates of HRV during the second and third trimester of pregnancy[11,12], while

one study found a decrease in spectral estimates of HRV in mature fetuses compared with immature fetuses[13]. This discrepancy might be explained from the fact that these studies did not account for fetal movement during the third trimester. Changes in fetal HRV due to fetal rest-activity state occur after 30 weeks of gestation[14]. Since spectral estimates of fetal HRV are known to be associated with rest-activity states at term gestation[10,12], it is difficult to interpret spectral values without classifying fetal movements.

By measuring LF and HF spectral power at regular time intervals during gestation, the development of the fetal autonomic cardiac control can be examined. We developed a new method to obtain the fetal ECG non-invasively from the maternal abdomen[15,16]. This method allows for beat-to-beat detection of the fetal R-waves and provides fetal beat-to-beat heart rate and spectral estimates non-invasively. The feasibility of this method to study the development of fetal autonomic cardiac control during gestation has not yet been investigated before.

The first objective of the current study is to present a non-invasive method for fetal ECG and beat-to-beat heart rate detection and to evaluate its clinical feasibility. The second objective is to study the relationship between GA and spectral estimates of fetal HRV and to study the influence of fetal rest-activity states on spectral estimates after 30 weeks of gestation.

Methods

Subjects

A prospective longitudinal study was performed in a tertiary-care teaching hospital. The study protocol was approved by the institutional review board at the Máxima Medical Centre, Veldhoven, the Netherlands. Patients were recruited consecutively from a healthy population, undergoing routine pregnancy follow up during one of the first outpatient visits. Only healthy women with an uneventful singleton pregnancy, not taking medication other than iron tablets or vitamins, were asked to participate before a GA of 12 weeks. Exclusion criteria were women under the age of 18 years and multiple pregnancies. Participants were included after a written informed consent form was signed. Pregnancy duration was determined from the last menstrual period and confirmed by crown rump length at 10 to 12 weeks of gestation. Pregnancies complicated by hypertension, preeclampsia, fetal growth restriction, premature labour, diabetes mellitus, or fetal congenital malformations after inclusion were excluded. Only pregnancies which progressed uneventfully resulting in the delivery of a healthy infant with a birthweight above the 10th percentile corrected for GA, maternal parity and fetal sex[17] were included in the data analysis.

Data acquisition and signal processing

Non-invasive fetal ECG measurements were repeatedly performed antenatally. A non-invasive electrophysiologic monitor for obstetrics (NEMO), shown in Figure 9.1, was used to record and store the electrical activity on the maternal abdomen.

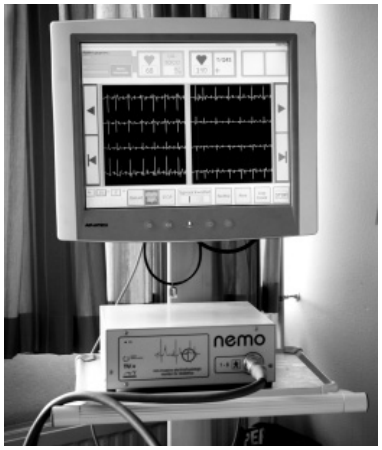


Figure 9.1. Prototype of the NEMO system.

The NEMO system was developed in the Máxima Medical Centre in cooperation with the Eindhoven University of Technology and Maastricht Instruments BV. The system was approved by the Medical Technical Service Department of the Máxima Medical Centre. Recordings were performed at approximately 14, 18, 22, 24, 26, 30, 34, 36, 38, and 40 weeks of gestation. Before starting a measurement, the woman's skin was prepared to reduce impedance by gentle excoriation of surface skin cells and by cleaning the skin with alcohol. Measurements were performed non-invasively using eight self-adhesive electrodes and one reference and one ground electrode on the maternal abdomen. The electrode configuration is shown in Figure 9.2.

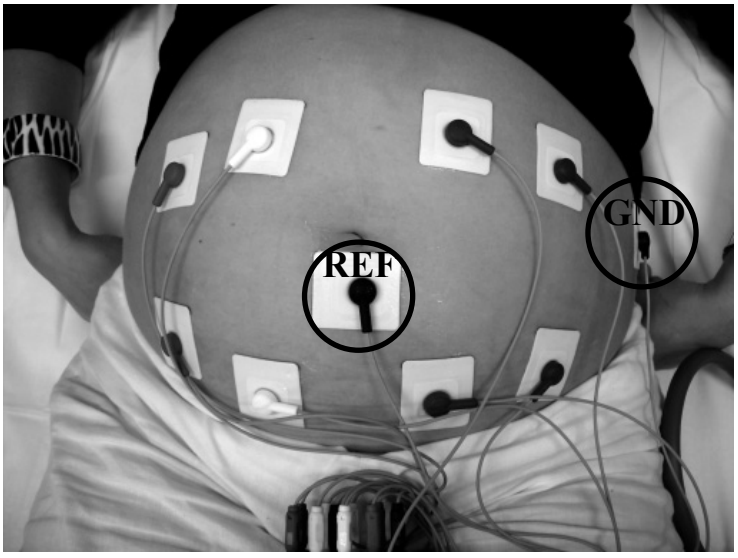


Figure 9.2. Electrode configuration for antepartum fetal ECG recording. GND: ground electrode. REF: reference electrode.

Each recording session took place between 8:00 h and 18:00 h, with the patient lying comfortable in a bed in semi recumbent position. During this time period, no important fluctuations in fetal HRV due to differences in time of the day were expected[18]. The electrode impedances were checked to ensure that they did not exceed 5 kΩ. The duration of recordings was approximately 45 minutes. Simultaneous ultrasound recordings (Aloka SSD-1000, Hitachi Aloka Medical, Tokyo, Japan) were performed to assess the fetal rest-activity state. Each fetus was visualised in a parasagittal plane. With the transducer in this position most of the fetal head and trunk and one or more limbs could be viewed.

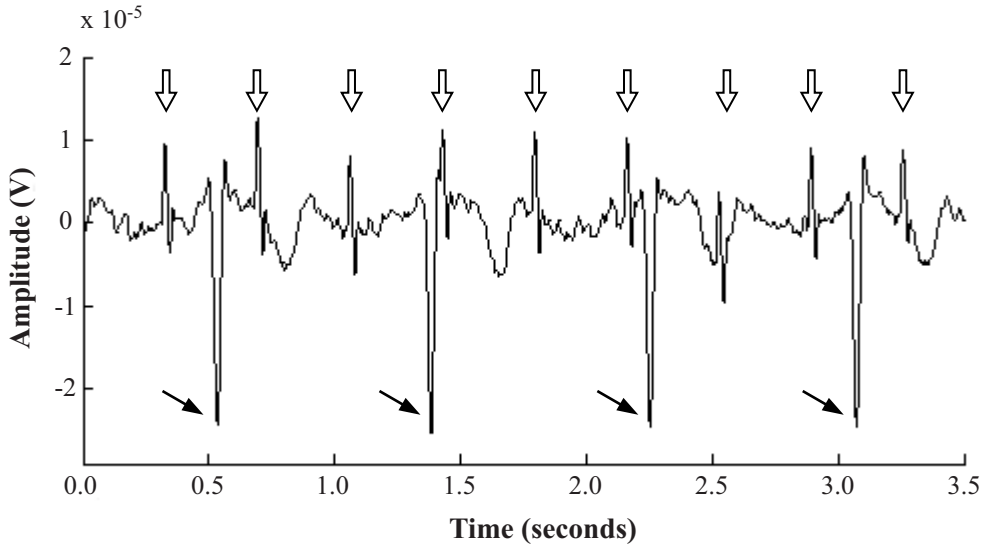


Figure 9.3. Filtered abdominal signal containing both maternal (↘) and fetal ECG (⇩).

The abdominal data were analysed off-line. The eight input signals were recorded with a sample frequency of 1000 Hz. The signals were bandpass filtered between 1.5 and 70 Hz in order to suppress high frequency noise and low frequency electronic drift. A 50 Hz notch filter was used to suppress power line interference. The maternal ECG waveform was estimated and subtracted from the signals, without affecting present fetal ECG complexes. This was done using a novel method that removed the maternal ECG by means of weighted averaging of maternal ECG segments[19]. Figure 9.3 shows an example of a filtered abdominal signal containing both maternal and fetal ECG. Figure 9.4 shows the signal after maternal ECG subtraction.

The eight resulting fetal ECG traces were processed to detect the beat-to-beat fetal heart rate. The signal-to-noise ratio of these signals is enhanced by spatially combining the signals[20]. R-peaks in the fetal ECG are detected and used to create the fetal beat-to-beat heart rate signals as described previously[20].

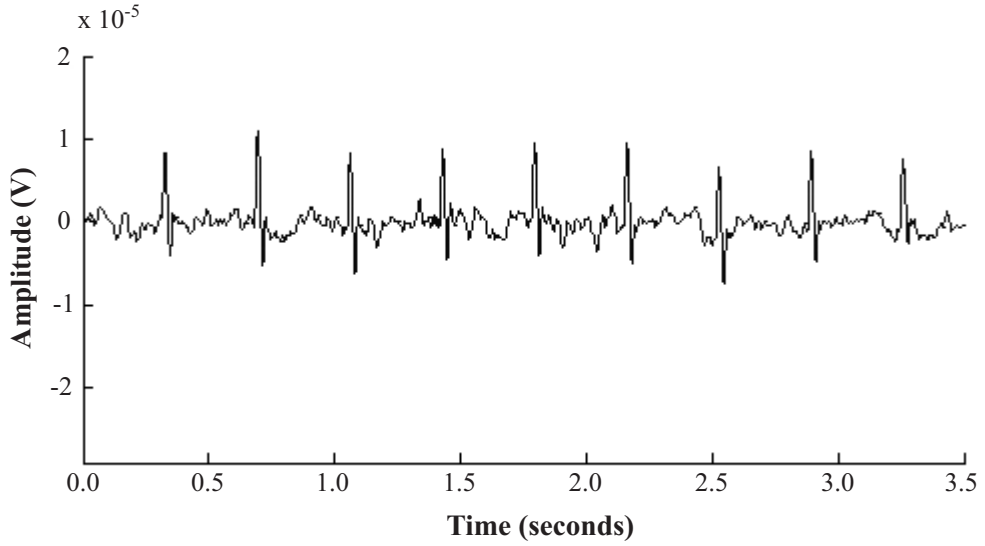


Figure 9.4. Filtered abdominal fetal signal after subtraction of the maternal ECG.

Spectral analysis

To prevent incorrect RR-intervals from dominating the spectrum, an RR-interval was automatically excluded if it exceeded the range of 0.2 to 1.3 seconds (46 to 300 beats per minute) or deviated more than 12% from preceding successive RR-intervals[9]. These incorrect RR-intervals were removed from the dataset and replaced by linear interpolation between the last preceding and the first succeeding correct RR-interval. From the beat-to-beat fetal heart rate data, 64-second segments were selected consecutively. To minimise the effect of artefact correction on the calculated spectral estimates, only segments with less than 5% artefact correction were included for analysis[21]. Visual inspection by an expert was performed to check for remaining artefacts, originating from misdetection of fetal R-peak. When a segment still contained an artefact, it was excluded for further analysis.

Spectral information about fetal beat-to-beat heart rate was obtained by using a Fourier transform. Beat-to-beat RR-intervals were resampled at 4 Hz and 256-point Fourier transforms were calculated for intervals of 64 seconds[22]. The direct current component was subtracted before calculating the Fourier transform. To reduce spectral leakage, the signal was multiplied with a Parzen window function. Based on previous studies[23], as well as the physiological range of fetal heart and respiratory movement rate, the following frequency bands were chosen: total frequency band: 0.04 to 1.5 Hz, LF: 0.04 to 0.15 Hz and HF: 0.4 to 1.5 Hz. Absolute spectral power values were expressed in squared milliseconds. After calculating the spectral power of fetal heart rate variability in these frequency bands, normalised values were calculated by dividing LF and HF power by total power.

Fetal rest-activity state

For each selected 64-second segment of fetal heart rate data, the corresponding ultrasound segment was analysed. All segments were divided into quiet sleep and active sleep, by visual inspection by a single observer with 8 years obstetric ultrasound experience. Assessment of fetal rest-activity states was based upon the presence or absence of fetal body movements. Body movements comprised the collective trunk, limb and head movements. When, after 34 weeks of gestation, the fetal rest-activity state could not be determined by ultrasound, the behavioural state was determined based on visual inspection of the fetal heart rate pattern as described by Nijhuis et al.[24]. In healthy fetuses from this GA, the relation between fetal movements and CTG pattern is so strong that the different states can be assessed reliably by visual identification of heart rate patterns alone[14].

Statistical methods

For each patient, for all available 64-second segments of heart rate data per GA group, median values were calculated for the absolute and normalised spectral power in the LF and the HF band. It is known that fetal ECG measurements are extremely difficult to obtain around 30 weeks of gestation due to the presence of the vernix caseosa, which electrically shields the fetus from its surroundings[25]. Since changes in fetal heart rate variability due to fetal rest-activity state only occur after 30 weeks of gestation[14], data were analysed separately for the periods below and above 30 weeks of gestation. The median spectral estimates were plotted as a function of GA. The median spectral values were normally distributed. Simple linear regression was used to study changes in spectral estimates over GA.

For the GA group above 30 weeks, analysis was repeated with restriction to fetal rest and activity, to examine the effect of fetal rest-activity state on the relation between spectral estimates and GA.

In addition, for the GA group above 30 weeks, the mean values of the median spectral estimates were compared during the active and quiet fetal state. For comparison between the active and quiet state an independent *t* test was used.

Statistical significance was assumed at an α level of 0.05.

Results

40 women were studied longitudinally during pregnancy. Measurements were performed from November 2006 up to August 2009. From the 40 patients under study, three patients were excluded because pregnancy was complicated by pregnancy induced hypertension. In addition, two patients were excluded because of preterm labour at a gestational age of respectively 31 and 32 weeks. The neonate born at 32 weeks of gestation was growth retarded (5th percentile for parity, GA and fetal sex) and had an anal atresia. From the remaining data, 330, 64-second segments of beat-to-beat heart rate data (2.75%) could

be used for spectral analysis. Figure 9.5 shows the percentage of usable segments, for the different GA groups.

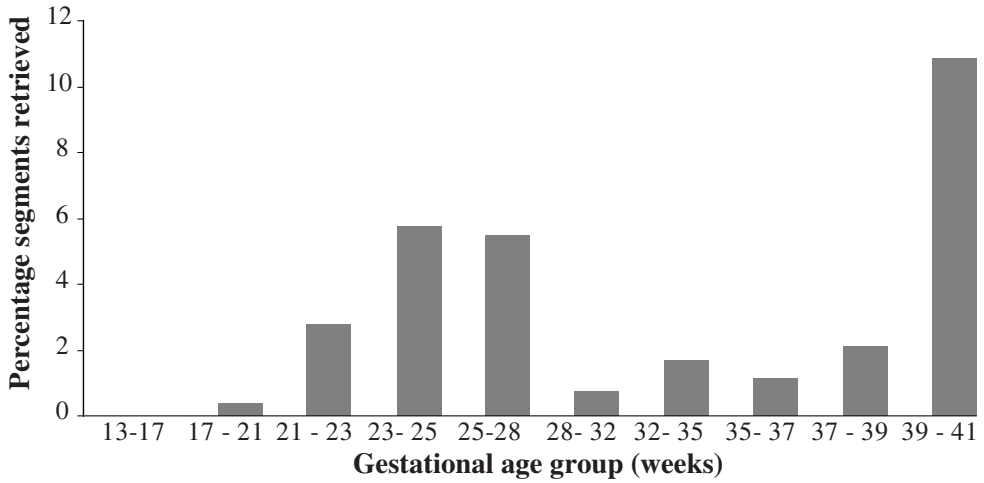


Figure 9.5. Percentage of 64-second segments, of beat-to-beat fetal heart rate data, that could be retrieved for Fourier transform, for each GA group.

The period between 17 and 21 weeks of gestation was excluded for further analysis since only five 64-second segments of heart rate data could be retrieved. Furthermore, no segment could be retrieved in the period between 30 and 34 weeks of gestation. In total, 325 segments remained for final analysis.

From the included 35 women, ten women were excluded because no good-quality fetal beat-to-beat heart rate could be retrieved from the abdominal recordings. For the remaining 25 women included for analysis, in total 213 abdominal measurements were performed (from which 325 segments could be used for analysis). The mean number of measurements per patient was 9 (standard deviation (sd) 1.6). The mean duration of each measurement was 42 minutes (sd 9). All mothers delivered at term. All neonates had a birthweight above the 10th percentile corrected for parity, GA and fetal sex. All neonates had an Apgar score of at least eight at 1 minute and at least nine at 5 minutes. All neonates had an umbilical artery pH > 7.05 and an umbilical artery base deficit ≤ 10. Patients' characteristics are shown in Table 9.1.

Figure 9.6 shows the absolute LF and HF power as a function of GA, for the GA period of 21 to 30 and 34 to 41 weeks. Linear regression lines were fitted to the data. A significant increase was seen in absolute LF and HF power, from 21 to 30 weeks of gestation. A non-significant decrease in LF and a non-significant increase in HF power were seen from 34 to 41 weeks of gestation.

Table 9.1. Characteristics of the patients included for analysis

	% or mean (standard deviation)
Maternal body mass index before pregnancy	23.6 (4.0)
Nulliparous	64%
Maternal age at birth (years)	32 (4)
Gestational age at birth (days)	279 (10)
Birthweight (grams)	3561 (543)
Apgar score at 5 minutes	10 (0.3)
Umbilical artery pH at birth	7.22 (0.08)
Umbilical artery base deficit at birth	7.3 (2.7)

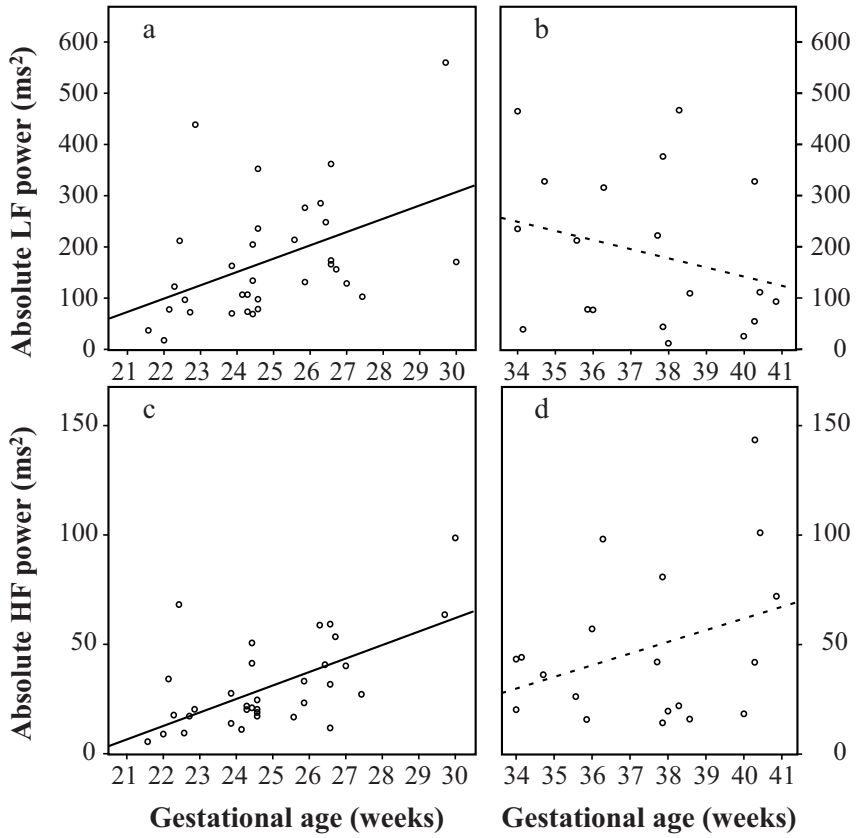


Figure 9.6. The association between absolute LF and HF power and GA, for the period of 21 to 30 and 34 to 41 weeks of gestation. a) R^2: 0.20 ($P = 0.009$), b) R^2: 0.08 ($P = 0.26$), c) R^2: 0.37 ($P = 0.0004$) and d) R^2: 0.12 ($P = 0.15$).

Figure 9.7 shows the normalised LF and HF power as a function of GA, for the GA period of 21 to 30 and 34 to 41 weeks. Linear regression lines were fitted to the data. For the normalised power, no significant trend was observed.

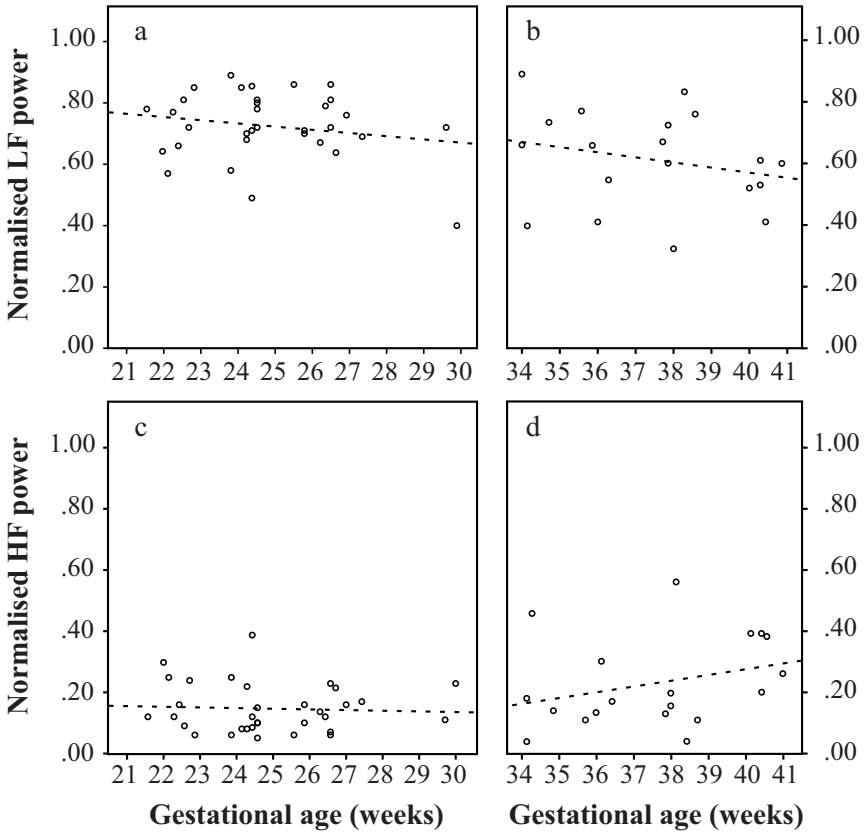


Figure 9.7. The association between normalised LF and HF power and GA, for the period of 21 to 30 and 34 to 41 weeks of gestation. a) R^2: 0.04 (P = 0.28), b) R^2: 0.06 (P = 0.31), c) R^2: 0.003 (P = 0.76) and d) R^2: 0.09 (P = 0.21).

From the available segments below 30 weeks of gestation, fetal rest-activity state could be determined based on ultrasound for 85 segments (43%). Of these, 86% was retrieved during the active state, while 14% was retrieved during the quiet state.

In the GA group of 34 to 41 weeks of gestation, rest-activity state could be classified based on ultrasound for 69 segments (54%). For the remaining 58 segments (46%), the state was assessed based on fetal heart rate pattern. From the selected segments, 38% was retrieved during active sleep and 62% during quiet sleep. Table 9.2 displays, the percentage of the selected segments in active sleep and quiet sleep for the different GA groups after 30 weeks of gestation.

Table 9.2. Percentage of segments with the fetus in the active state and in rest, for the GA groups after 30 weeks of gestation

GA	Active sleep	Quiet sleep
34-36	70%	30%
36-38	43%	57%
38-40	32%	68%
40-41	28%	72%

Table 9.3 shows the mean values of the median absolute and normalised LF and HF power, for the active and quiet state, for 34 to 41 weeks of gestation. During the active state, absolute and normalised LF power were significantly higher compared to the quiet state. During the quiet state, normalised HF power was significantly higher. To guarantee no bias was introduced by assessment of fetal rest-activity state by fetal heart rate pattern, the analysis was repeated for segments for which rest-activity state was solely assessed based on ultrasound. The results (not shown) were highly comparable and remained significant.

Table 9.3. Mean values of the median absolute and normalised LF and HF power for the active and quiet sleep state for the GA period of 34 to 41 weeks

	Active sleep	Quiet sleep	*P*-value
Absolute LF (ms^2)	555	151	0.002
Absolute HF (ms^2)	62	38	0.09
Normalised LF	0.77	0.59	0.005
Normalised HF	0.10	0.26	0.002

To study the effect of fetal behaviour on spectral estimates, the association between spectral estimates and GA was studied for rest and activity separately, for the GA period above 30 weeks. Figure 9.8 shows the absolute LF and HF power as a function of GA for the active and quiet sleep state. Linear regression lines were fitted to the data.

During the active sleep state, a non-significant increase in absolute LF and HF power was observed with progress of pregnancy. No (significant) trend was observed in normalised values during the active sleep state (results not shown). During the quiet sleep state, a non-significant decrease in absolute LF power and a non-significant increase in absolute HF power were observed. For the normalised values during the quiet sleep state a comparable (non-significant) trend was shown as for the absolute values (results not shown).

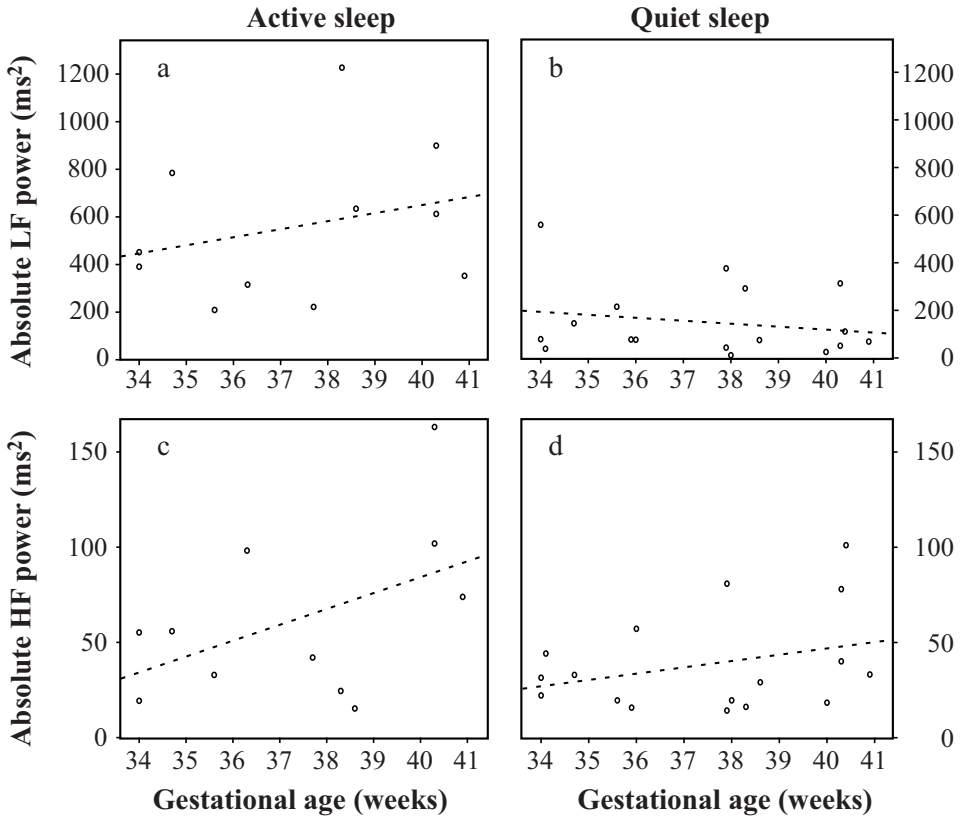


Figure 9.8. The association between the absolute LF and HF power and GA, for the active and quiet sleep state, for the period of 34 to 41 weeks of gestation. a) R^2: 0.08 (P = 0.41), b) R^2: 0.04 (P = 0.44), c) R^2: 0.23 (P = 0.14) and d) R^2: 0.10 (P = 0.22).

Discussion

Our group has developed a new method for non-invasive fetal ECG measurement[19,20]. This new method can be used during periods in pregnancy, in which other (invasive) techniques cannot be used for monitoring. Our results in a large study group showed that it is possible, yet difficult, to retrieve fetal beat-to-beat heart rate from non-invasive abdominal fetal ECG measurements. Spectral analysis was feasible in approximately 3% of abdominal data and thus further improvements need to be made in signal processing. We were not capable of retrieving fetal beat-to-beat heart rate from the abdominal measurements before 18 weeks and between 30 and 34 weeks of gestation. Below 18 weeks this was probably due to the small size of the fetal heart. This results in very low amplitude of the fetal ECG, rendering it undetectable on the maternal abdomen. Between 30 and 34 weeks of gestation, the presence of the vernix caseosa, which electrically isolates the fetal heart[25], probably caused for significant attenuation of the

ECG signal. During the very preterm period (21 to 28 weeks), approximately 5% of data was suitable for spectral analysis. At term, approximately 7% of data was suitable for spectral analysis. Probably, during the term period the disappearance of the vernix caseosa and the relatively large fetal heart, made it easier to detect the fetal signal from the combined fetal-maternal signals measured on the maternal abdomen.

Very preterm period (21 to 30 weeks of gestation)

For the very preterm period we observed a significant increase in absolute LF and HF power of fetal heart rate variability with progressing pregnancy. We hypothesise that this increase was due to increased sympathetic and parasympathetic modulation of the fetal heart resulting from maturation of the fetal autonomic nervous system. This is in accordance with animal studies that showed an increase in sympathetic and parasympathetic cardiac modulation in premature fetuses compared to immature fetuses[26].

It is unlikely that that the observed changes in spectral estimates before 30 weeks of gestation were due to changes in fetal breathing movements or rest-activity state. Although fetal breathing movements occurred as early as 10 weeks of gestation[27], the high frequency peak that was observed during breathing at term[28], could not be observed at 26 weeks of gestation[29]. In addition, the incidence of fetal breathing movements did not change between 24 and 28 weeks of gestation[30]. The incidence of fetal movements decreased as pregnancy progresses[31]. From 24 to 28 weeks of gestation a healthy fetus on average made 150 to 200 movements each hour[31]. Therefore, it was expected that most selected 64-second segments of heart rate data below 30 weeks were measured during fetal activity, as was confirmed by our analysis of the corresponding ultrasound measurements. In addition, in term fetuses during the active state, LF power was high compared to quiescence[10]. Although short rest-activity cycles were first noticed at 23 weeks of gestation, fetal heart rate variability was similar during fetal activity and rest up to 30 weeks of gestation[14] and behavioural states could not be observed[32].

The observed increase in absolute LF and HF power was not reflected in the normalised values during the very preterm period. This might be due to a comparable relative increase in both absolute LF and HF power and to the relatively dominant sympathetic system in premature fetuses. This was reflected in the high normalised LF power and is in accordance with animal studies that have shown that the sympathetic tone predominates over the parasympathetic tone during the intrauterine life[26].

The (near) term period (34 to 41 weeks of gestation)

For the (near) term fetuses a non-significant decrease in absolute LF and a non-significant increase in absolute HF power were observed. A LF power decrease, after 30 weeks was also described by David et al.[12]. Fetal activity is known to increase fetal HRV from approximately 30 weeks of gestation onwards[14], and a decrease in fetal movements with GA was reported[31]. Therefore, a LF power decrease after 30 weeks, is expected to occur due to a decrease in fetal movements. Later in pregnancy, starting in the 34th week of gestation, fetal behavioural states appear[33]. As these states are partly defined on the basis of HRV, it seems relevant to consider them in the interpretation of HRV measures.

Furthermore, absolute and normalised LF power were found significantly higher and normalised HF power significantly lower during fetal activity compared to rest. A non-significant increase in absolute HF power was observed during the active state. These results were similar to those obtained with invasive measurements during labour at term[10].

If analysis was repeated with restriction to periods of fetal rest and activity (as shown in Figure 9.8), LF power increased non-significantly as a function of GA during activity, while LF power decreased non-significantly during rest. Since for the selected segments the time spent in rest increased with GA during the (near) term period (as shown in Table 9.2), a decrease in fetal activity might explain the overall decrease in LF power as pregnancy progresses.

During fetal activity, the observed non-significant increase in absolute LF power, with advancing gestational age, might be due to a more mature autonomic nervous system, which is capable of adapting to increased metabolic demands during fetal activity. This might be a sign of autonomic functional development. However, since the trend was not significant, probably due to the limited number of usable segments, further study is necessary to confirm this hypothesis.

An increase in absolute and normalised HF power was found, in our studies, for invasive measurements during the term period during labour[10]. We observed a similar trend towards increased absolute and normalised HF power near term, in the present study. Because this trend was independent of fetal rest-activity state, it cannot be explained by changes in fetal behaviour. This trend might suggest continuing parasympathetic maturation during the term period and increasing influence of the vagal system. This is in line with Assali et al., who found a marked rise in parasympathetic tone during the neonatal period and up until the adult state[26].

For the selected segments of heart rate data in the current study, for the (near) term fetuses, 62% was in quiet sleep and 38% was in active sleep. Previous studies reported that the quiet sleep state accounts for approximately 30% and the active sleep state for 60% of the behaviour of term fetuses and that awake states appear rarely[34]. Therefore, it seems that fetal heart rate detection is more successful during rest, due to fewer disturbances caused by motion artefacts.

Limitations

The main limitation of the presented study is the very small percentage of available signals suitable for analysis. However, our new method is one of the first by which fetal HRV studies can be performed non-invasively based on indirect fetal ECG measurement. In addition, we prefer to obtain good-quality data over a high quantity of data to make sure reliable results are obtained. Improvement of both equipment and algorithm is still necessary to obtain more good-quality data. Furthermore, due to the limited amount of data for analysis, we were unable to analyse inter- and intraindividual variation in the relation of spectral estimates with GA, although the study set-up was longitudinal. In

addition, due to missing data and large ranges of individual spectral estimates, statistical significance was often not reached. Therefore, we were careful in drawing conclusions on maturational aspects, although trends were visible.

Conclusions

Our non-invasive fetal ECG method enables to measure fetal HRV in frequency-domain during the very preterm and the term period. The observed changes during the premature period are in accordance with those seen in animal studies and our results in the (near) term period are fully in accordance with the previous literature on invasive measurements during labour at term. This is the first study that measures spectral estimates longitudinally and relates spectral estimates to fetal state. Further progress in signal processing will enable improved study of the relation between spectral estimates and GA and allow for longitudinal analysis.

References

1. Alfirevic Z, Devane D, Gyte GM. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. Cochrane Database Syst Rev 2008.
2. Neilson JP. Fetal electrocardiogram (ECG) for fetal monitoring during labour. Cochrane Database Syst Rev 2011.
3. Mahendru AA, Lees CC. Is intrapartum fetal blood sampling a gold standard diagnostic tool for fetal distress? Eur J Obstet Gynecol Reprod Biol 2011;156:137-139.
4. Goodwin TM, Milner-Masterson L, Paul RH. Elimination of fetal scalp blood sampling on a large clinical service. Obstet Gynecol 1994;83:971-974.
5. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-1065.
6. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213: 220-222.
7. Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Välimäki IA, Rosén KG, Ekholm EM. Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. BJOG 2005;112:418-423.
8. van Laar JO, Peters CH, Vullings R, Houterman S, Bergmans JW, Oei SG. Fetal autonomic response to severe acidaemia during labour. BJOG 2010;117:429-437.
9. van Laar JO, Peters CH, Houterman S, Wijn PF, Kwee A, Oei SG. Normalized spectral power of fetal heart rate variability is associated with fetal scalp blood pH. Early Hum Dev 2011;87:259-263.
10. van Laar JO, Peters CH, Vullings R, Houterman S, Oei SG. Power spectrum analysis of fetal heart rate variability at near term and post term gestation during active sleep and quiet sleep. Early Hum Dev 2009;85:795-798
11. van Leeuwen P, Geue D, Lange S, Hatzmann W, Gronemeyer D. Changes in the frequency power spectrum of fetal heart rate in the course of pregnancy. Prenat Diagn 2003;23:909-916.
12. David M, Hirsch M, Karin J, Toledo E, Akselrod S. An estimate of fetal autonomic state by time-frequency analysis of fetal heart rate variability. J Appl Physiol 2007;102:1057-1064.
13. Karin J, Hirsch M, Akselrod S. An estimate of fetal autonomic state by spectral analysis of fetal heart rate fluctuations. Pediatr Res 1993;34:134-138.
14. Pillai M, James D. The development of fetal heart rate patterns during normal pregnancy. Obstet Gynecol 1990;76:812-816.
15. Vullings R. Non-invasive fetal electrocardiogram: analysis and interpretation. PhD Thesis, Eindhoven University of Technology, Eindhoven, 2010.
16. Peters CH. Time-scale analysis of antepartum fetal heart rate variability. PhD Thesis, Eindhoven University of Technology, Eindhoven, 2011.
17. Visser GH, Eilers PH, Elferink-Stinkens PM, Merkus HM, Wit JM. New Dutch reference curves for birthweight by gestational age. Early Hum Dev 2009;85:737-744.
18. Lange S, van Leeuwen P, Geue D, Hatzmann W, Grönemeyer D. Influence of gestational age, heart rate, gender and time of day on fetal heart rate variability. Med Biol Eng Comput 2005;43:481-486.
19. Vullings R, Peters CH, Sluijter R, Mischi M, Oei SG, Bergmans JW. Dynamic segmentation and linear prediction for maternal ECG removal in antenatal abdominal recordings. Physiol Meas 2009;30: 291-307.

20. Vullings R, Peters CH, Hermans MJ, Wijn PF, Oei SG, Bergmans JW. A robust physiology-based source separation method for QRS detection in low amplitude fetal ECG recordings. Physiol Meas 2010;31:935-951.
21. Peters C, Vullings R, Bergmans J, Oei G, Wijn P. The effect of artifact correction on spectral estimates of heart rate variability. Conf Proc IEEE Eng Med Biol Soc 2008:2669-2672.
22. Peters CH, ten Broeke ED, Andriessen P, Vermeulen B, Berendsen RC, Wijn PF, Oei SG. Beat-to-beat detection of fetal heart rate: Doppler ultrasound cardiotocography compared to direct ECG cardiotocography in time and frequency domain. Physiol Meas 2004;25:585-593.
23. de Beer NA, Andriessen P, Berendsen RC, Oei SG, Wijn PF, Bambang Oetomo S. Customized spectral band analysis compared with conventional Fourier analysis of heart rate variability in neonates. Physiol Meas 2004;25:1385-1395.
24. Nijhuis JG, Prechtl HF, Martin CB, Bots RS. Are there behavioural states in the human fetus? Early Hum Dev 1982;6:177-195.
25. Oostendorp TF, van Oosterom A, Jongsma HW. The effect of changes in the conductive medium on the fetal ECG throughout gestation. Clin Phys Physiol Meas 1989;10 Suppl B:11-20.
26. Assali NS, Brinkman CR, Woods JR, Dandavino A, Nuwayhid B. Development of neurohumoral control of fetal, neonatal, and adult cardiovascular functions. Am J Obstet Gynecol 1977;129: 748-759.
27. de Vries JI, Visser GH, Prechtl HF. The emergence of fetal behavior. I. Qualitative aspects. Early Hum dev 1982;7:301-322.
28. Divon MY, Yeh SY, Zimmer EZ, Platt LD, Paldi E, Paul RH. Respiratory sinus arrhythmia in the human fetus. Am J Obstet Gynecol 1985;151:425-428.
29. Ferrazzi E, Pardi G, Setti PL, Rodolfi M, Civardi S, Cerutti S. Power spectral analysis of the heart rate of the human fetus at 26 and 36 weeks of gestation. Clin Phys Physiol Meas 1989;10 Suppl B:57-60.
30. Natale R, Nasello-Paterson C, Connors G. Patterns of fetal breathing activity in the human fetus at 24 to 28 weeks of gestation. Am J Obstet Gynecol 1988;158:317-321.
31. ten Hof J, Nijhuis IJ, Mulder EJ, Nijhuis JG, Narayan H, Taylor DJ, Westers P, Visser GH. Longitudinal study of fetal body movements: nomograms, intrafetal consistency, and relationship with episodes of heart rate patterns a and B. Pediatr Res 2002;52:568-575.
32. Drogtrop AP, Ubels R, Nijhuis JG. The association between fetal body movements, eye movements and heart rate patterns in pregnancies between 25 and 30 weeks of gestation. Early Hum Dev 1990;23:67-73.
33. Nijhuis IJ, ten Hof J, Nijhuis JG, Mulder EJ, Narayan H, Taylor DJ, Visser GH. Temporal organization of fetal behavior from 24-weeks gestation onwards in normal and complicated pregnancies. Dev Psychobiol 1999;34:257-268.
34. Pillai M, James D. Behavioural states in normal mature human fetuses. Arch Dis Child 1990;65: 39-43.

Chapter 10

Summary and general discussion

Summary

Fetal autonomic cardiac response during pregnancy and labour

Timely recognition of fetal distress, during pregnancy and labour, in order to intervene adequately is of major importance to avoid neonatal morbidity and mortality. As discussed in **chapter 1**, the cardiotocogram (CTG) might be a useful screening test for fetal monitoring but it has insufficient specificity and requires additional diagnostic tests in case of suspected fetal compromise to avoid unnecessary operative deliveries. Potential additional techniques used in clinical practice are fetal scalp blood sampling (FBS) and ST-waveform analysis of the fetal electrocardiogram (ECG; STAN®). However, publications on these techniques provide limited support for the use of these methods in the presence of a non-reassuring CTG for reducing caesarean sections. In addition, these techniques are invasive and can therefore only be used during labour at the term or the near term period. Consequently, it is of great clinical importance that additional methods are developed that contribute to more reliable assessment of fetal condition. Preferably, this information is obtained non-invasively.

Valuable additional information on the fetal condition can possibly be obtained by spectral analysis of fetal heart rate variability (HRV). The fetal heart rate fluctuates under the control of the autonomic part of the central nervous system. The autonomic cardiac modulation is discussed in **chapter 2**. The sympathetic and parasympathetic nervous systems typically operate on partly different timescales. Time-frequency analysis (spectral analysis) of fetal beat-to-beat HRV can hence quantify sympathetic and parasympathetic modulation and characterise autonomic cardiac control[1]. The low frequency (LF) component of HRV is associated with both sympathetic and parasympathetic modulation while the high frequency (HF) component is associated with parasympathetic modulation only[2]. Spectral estimates of HRV might indirectly reflect fetal wellbeing and increase insight in the human fetal autonomic cardiac response. In **chapter 3**, technical details for retrieving fetal beat-to-beat heart rate and its spectral estimates are provided.

In this thesis spectral analysis of fetal HRV is investigated. The first objective is to study the value of spectral analysis of fetal HRV as a tool to assess fetal wellbeing during labour at term. The second objective is to monitor spectral estimates of fetal HRV, non-invasively, during gestation to increase insight in the development of human fetal autonomic cardiac control.

Since Akselrod reported the relation between autonomic nervous system modulation and LF and HF peaks in frequency-domain[1], frequency analysis of RR-interval fluctuations is widely performed[2]. For human adults, standards for HRV measurement and physiological interpretation have been developed[2]. Although HRV parameters are reported to be highly prognostic in human adults in case of cardiac disease, little research is done towards the value of these parameters in assessing fetal distress in the human fetus, as shown in **chapter 4**. In this chapter, the literature about time-frequency analysis of human fetal HRV is reviewed in order to determine the value of spectral estimates

for fetal surveillance. Articles that described spectral analysis of human fetal HRV and compared the energy in spectral bands with fetal blood-gas values were included. Only six studies met our inclusion criteria. One study found an initial increase in LF power during the first stage of fetal compromise, which was thought to point to stress-induced sympathetic hyperactivity[3]. Five out of six studies showed a decrease in LF power in case of fetal distress[3,4,5,6,7]. This decrease in LF power in case of severe fetal compromise was thought to be the result of immaturity or decompensation of the fetal autonomic nervous system. These findings support the hypothesis that spectral analysis of fetal HRV might be a promising method for fetal surveillance.

All studies included in the literature review used absolute values of LF and HF power. Although absolute LF and HF power of HRV provide useful information on autonomic modulation, especially when considering fetal autonomic development, LF and HF power may also be measured in normalised units. Normalised LF (LFn) and normalised HF power (HFn) of HRV represent the relative value of each power component in proportion to the total power[2]. Adrenergic stimulation can cause a sympathetically-modulated increase in fetal heart rate[8]. A negative correlation however exists between heart rate and HRV[9]. As a result, the sympathetic stimulation can decrease the total power of HRV and even the absolute LF power. When normalising the absolute LF (and HF) with respect to the total power, a shift in activity from HFn to LFn might become visible, revealing the expected underlying sympathetic activity. Thus, because changes in total power influence absolute spectral estimates in the same direction, normalised values of LF and HF power seem more suitable for fetal monitoring. In other words, normalised spectral estimates detect relative changes that are no longer masked by changes in total power[2]. LFn and HFn power are calculated by dividing LF and HF power, respectively, by total power and represent the controlled and balanced behaviour of the two branches of the autonomic nervous system[2]. In **chapter 5** we hypothesised that the autonomic cardiovascular control is functional in fetuses at term, and that LFn power increases in case of distress due to increased sympathetic modulation. During labour at term, ten acidaemic fetuses were compared with ten healthy fetuses. During the last 30 minutes of labour, acidaemic fetuses had significantly higher LFn power and lower HFn power than control fetuses, which points to increased sympathetic modulation. No differences in absolute LF or HF power were found between both groups. The observed differences in normalised spectral estimates of HRV were not observed earlier in labour. In conclusion, it seems that the autonomic nervous system of human fetuses at term responds adequately to severe stress during labour. Normalised spectral estimates of HRV might be able to discriminate between normal and abnormal fetal condition.

Although we found significant differences in normalised spectral estimates between healthy and acidaemic fetuses, we wondered whether spectral power of HRV is also related to fetal distress in an earlier stage. The next step in **chapter 6** was therefore, to investigate whether spectral estimates are related to fetal scalp blood pH during labour. Term fetuses during labour, in cephalic presentation, that underwent one or more scalp blood samples were studied. Beat-to-beat fetal heart rate segments, preceding the scalp blood measurement, were used to calculate spectral estimates. In total 39 FBS from 30

patients were studied. We found that normalised spectral estimates are related to fetal scalp blood pH while absolute spectral estimates are not related to fetal pH. It was further demonstrated that LFn power is negatively related and HFn power is positively related to fetal pH. These findings point to increased sympathetic and decreased parasympathetic cardiac modulation in human fetuses at term upon decrease of their pH value. This study confirms the hypothesis that normalised spectral values of fetal HRV are related to fetal distress in an early stage.

Previous studies showed that absolute LF and HF power increase as pregnancy progresses, which is attributed to fetal autonomic maturation[10,11]. Since it is yet unclear how LFn and HFn evolve with progressing pregnancy, before using spectral analysis for fetal monitoring, it has to be determined whether gestational age has to be corrected for. In addition, fetal autonomic fluctuations, and thus spectral estimates of HRV, are influenced by fetal behavioural state[12]. Since these states continue to change during labour[13], thorough understanding of the way in which these changes in state influence spectral power is necessary for the interpretation of spectral values during labour at term. Therefore, in **chapter 7**, we examined whether differences in spectral estimates exist between healthy near term and post term fetuses during labour. In case such differences do exist, they should be taken into consideration for fetal monitoring. The quiet and active sleep states were studied separately to determine the influence of fetal behavioural state on spectral estimates of HRV during labour around term. No significant differences in spectral estimates were found between near term and post term fetuses during active sleep. During quiet sleep, LFn power was lower and HF and HFn power were higher in post term compared to near term fetuses, no significant differences in LF power were observed between both groups. LF, HF and LFn power were higher and HFn power was lower during active sleep compared to quiet sleep in both groups. This seems to point to sympathetic predominance during the active state in fetuses around term. In addition, post term parasympathetic modulation during rest seems increased compared to near term. In conclusion, fetal behavioural state and gestational age cause a considerable variability in spectral estimates in fetuses during labour, around term, which should be taken into consideration when using spectral estimates for fetal monitoring.

In chapters 4 to 6, spectral estimates of beat-to-beat fetal HRV were studied using fetal ECG recordings that were obtained directly from the fetal scalp during labour. However, the second objective of this thesis is to obtain spectral estimates non-invasively during gestation to increase insight in the development of human fetal autonomic cardiac control. The fetal ECG is also present on the maternal abdomen, although much smaller in amplitude and obscured by the maternal ECG and noise. **Chapter 8** focused on non-invasive measurement of the fetal ECG from the maternal abdomen. These measurements allow for obtaining beat-to-beat fetal heart rate non-invasively. Therefore, this method can be used to obtain spectral estimates of fetal HRV throughout gestation. Although abdominal recording of the fetal ECG may offer valuable additional information, it is troubled by poor signal-to-noise ratios (SNR) during certain parts of pregnancy, e.g. during the immature period and during the vernix period. To increase the usability of abdominal fetal ECG recordings, an algorithm was developed that uses a priori knowledge

on the physiology of the fetal heart to enhance the fetal ECG components in multi-lead abdominal fetal ECG recordings, before QRS detection. Evaluation of the method on generated fetal ECG recordings with controlled SNR showed excellent results.

The method for non-invasive fetal ECG and beat-to-beat heart rate detection presented in chapter 8 was used for analysis in **chapter 9**. The feasibility of this method in a longitudinal patient study was investigated. In addition, changes in spectral estimates of HRV during pregnancy were studied and related to fetal rest-activity state to study the development of fetal autonomic cardiac control. We found that approximately 3% of non-invasive fetal ECG recordings could be used for spectral analysis. Therefore, improvement of both equipment and algorithms is still needed to obtain more good-quality data. The percentage of successfully retrieved data depends on gestational age. Before 18 and between 30 and 34 weeks no good-quality beat-to-beat heart rate data were available. We found an increase in LF and HF power of fetal HRV with increasing gestational age, between 21 to 30 weeks of gestation. This increase in LF and HF power of HRV is probably due to increased sympathetic and parasympathetic modulation and might be a sign of autonomic development. Furthermore, we found sympathetic predominance during the active state compared to the quiet state in (near) term fetuses (34 to 41 weeks of gestation), comparable to the results observed during labour around term. During 34 to 41 weeks a (non-significant) decrease in LF and LFn power and a (non-significant) increase in HF and HFn power were observed. These non-significant changes in spectral estimates in near term fetuses might be associated with changes in fetal rest-activity state and increased parasympathetic modulation as pregnancy progresses. However, more research is needed to confirm this.

Clinical implications and future directions

The results of the fundamental research reported in this thesis show that spectral estimates of fetal HRV during labour around term are related to fetal condition. It was confirmed that normalised spectral values of fetal HRV cannot only discriminate between severe fetal acidaemia and normal fetal condition but are also related to fetal distress at an early stage. Obviously, these results need to be confirmed by large scale studies. Larger prospective studies are needed to determine cut-off values for clinical decision making and to determine the exact diagnostic value of spectral analysis for the identification of fetuses at risk for severe acidosis. We suggest that gestational age and behavioural state is taken into consideration for determining cut-off values.

Our non-invasive fetal ECG method enables to study fetal HRV parameters in frequency-domain during the very preterm and the (near) term period. The observed changes in these parameters during the preterm period are in accordance with those seen in animal studies and our results in the (near) term period are fully in accordance with our findings in invasive measurements during labour at term. However, further progress in signal processing needs to be made to obtain more good-quality, non-invasive beat-to-beat heart rate data.

In conclusion, although we made progress in the understanding of the fetal autonomic cardiac response during pregnancy and labour, the level of knowledge on this topic is still quite limited and, although we believe that the results are promising, they are not yet clinically applicable.

Methodology

Dawes et al. reported that the most useful sign of deteriorating fetal health is a progressive reduction in fetal HRV[14]. They calculated long term and short term variation (LTV and STV, respectively). LTV is a measure of the minute-by-minute fluctuations of the fetal heart rate around the baseline (in ms). STV is calculated as follows; each minute of the heart rate recording is divided into 16, 3.75-second epochs, the average pulse interval in each epoch is calculated, and the change in these average values from one section to the next determines the STV (in ms)[14]. These parameters are probably associated with autonomic modulation. However, for short recordings frequency-domain measures are preferred over time-domain measures, because more knowledge exists on the physiological interpretation[2]. Therefore, we prefer to study spectral estimates of fetal HRV, because these parameters, based on physiological grounds, clearly reflect sympathetic and parasympathetic modulation.

It is of great importance for further research that the method for spectral analysis of fetal HRV is standardised to enable comparability, reproducibility, reliable physiological interpretation and clinical applicability. When studying fetal surveillance we found that normalised spectral estimates are associated with fetal condition while absolute values are not[15,16]. When studying fetal behaviour or autonomic maturation both absolute and normalised spectral estimates provide additional information. Therefore, we believe that future studies should provide both absolute and normalised spectral estimates of HRV in order to completely describe the distribution of power in spectral components[2].

In addition, currently, most studies calculate spectral estimates off-line. To increase clinical applicability, future studies should focus on real-time monitoring, enabling timely intervention in case of fetal distress.

Spectral analysis of fetal HRV by means of the Fourier transform is sensitive to artefacts. Fetal heart rate data in clinical practice will regularly be corrupted by artefacts. Although LF parameters can be calculated accurately when up to 30% of RR-interval series is replaced by interpolated values, power in the HF range cannot be calculated reliably when over 5% of heart rate data is interpolated[17,18]. Fourier analysis is therefore only suitable for time-frequency analysis of heart rate data that are almost entirely free of artefacts. A possible solution for this limitation is the use of alternative methods for spectral analysis. Wavelet analysis, for example, enables analysis of powers in the HF range at a shorter time scale than Fourier analysis does. Short segments of heart rate data that are free of artefacts can then be used to calculate powers in the HF range reliably, while segments that contain artefacts can be excluded. By using this approach, HF spectral parameters can be calculated reliably even when large parts of data (up to 50%) are missing due to artefacts[18]. However, compared to Fourier transform, the calculation

of spectral parameters in the LF range with wavelet analysis is more sensitive to artefacts but still acceptable for levels of artefact correction of up to 20%[18]. This 20% cut-off also holds for the reliable estimation of normalised spectral values[18].

Another advantage of wavelet transform is that it allows analysis of non-stationary signals, while a Fourier transform assumes stationary signals with identical spectral characteristics throughout the analysis window. Obviously, in human fetuses signal stability cannot be ensured, because fetuses show rapid fluctuations in HRV, for example, due to immature autonomic regulation or adaptation to transient hypoxaemia during labour. Therefore, the resulting Fourier spectrum will be an average spectrum over the entire analysis window. When short segments are used, this limitation for fetal monitoring is overcome.

Additional value of spectral estimates of fetal HRV

Predicting fetal distress

We found that normalised spectral estimates of fetal HRV are related to fetal scalp blood pH value. In our hospital, from the obtained scalp blood samples only pH values were provided. As a result, no differentiation could be made between respiratory and metabolic acidosis, nor could samples with an artificially increased pH due to CO_2 loss be identified and excluded. It has been reported that neonatal complications are associated with metabolic rather than respiratory acidosis[19]. Respiratory acidosis occurs in the early stages of impaired blood supply to the fetus; hypoxaemia and hypercapnia occur, leading to a reduction in pH with a normal base excess. This is a common feature of labour. If hypoxia is prolonged, anaerobic metabolism is initiated and base deficit (BD) rises secondary to the presence of lactic acidosis. Lactate is the end product of anaerobic metabolism and it has been shown that lactate in FBS is a better marker for metabolic acidosis than pH or BD[20]. The above mentioned limitations might have influenced the relation we found between spectral estimates of HRV and fetal scalp blood pH values. Probably, spectral estimates are even better related to fetal scalp blood lactate values, as these lactate values more reliably reflect metabolic acidosis. It is therefore interesting to perform a prospective study to determine the value of spectral estimates of fetal HRV to predict fetal scalp blood lactate values. When a good correlation exists, one might speculate that spectral estimates might replace FBS in the future, as spectral analysis is non-invasive and provides information continuously. Obviously, such correlation should first be confirmed by more extensive analysis.

The STAN® technology, like FBS, depends on CTG interpretation, which is rather subjective. Probably, spectral estimates can support CTG interpretation, achieving more objective CTG classification, in addition to the STAN® technology, in the future. Spectral analysis objectively quantifies changes in fetal HRV that cannot always be detected by visual interpretation of fetal heart rate tracings. In addition, metabolic changes in the heart muscle are reflected as ST-changes in fetal ECG, but ST-changes may also be seen in non-hypoxic fetuses as a consequence of arousal reactions. Siira et al. found that a relative change in LF/HF ratio, greater than 30%, in combination with a significant

ST-event better predicts cord arterial metabolic acidosis than significant ST-events alone[21]. Hence, it is shown that spectral estimates provide additional information on fetal wellbeing and help differentiate between physiologic ST-changes and hypoxic ST-changes. This additional information may help to prevent unnecessary operational deliveries. However, this should be confirmed by larger studies.

In the meantime, to further improve the potential of spectral estimates for early detection of fetal distress, more insight in autonomic cardiac modulation must be gained. At first, normal values for absolute and normalised spectral power in the LF and HF band, in relation to gestational age and fetal behavioural state, should be determined. This should be done for the antepartum and for the intrapartum period separately, since the fetal autonomic nervous system responds to (temporary) hypoxaemia induced by uterine contractions during labour. Antepartum measurements provide insight into fetal autonomic nervous system development and maturation. The non-invasive method for beat-to-beat heart rate detection, based on maternal ECG removal and fetal ECG extraction, provides the opportunity for future research to gain this insight. Non-invasive spectral information might also contribute to a more reliable assessment of fetal condition in stages of pregnancy earlier than labour. This can be useful for monitoring high risk pregnancies e.g. intrauterine growth restricted fetuses or fetuses from mothers with diabetes. More information on fetal wellbeing will be extremely useful antepartum in premature fetuses, because, unnecessary medical interventions preterm can result in iatrogenic preterm births, and can lead to infant death[22]. On the other hand, an adverse acid-base status at birth due to late or no intervention is an additive risk factor to the effect of gestational age for neurological impairment in premature infants[23]. Ultimately, spectral information may help to make treatment decisions around the edge of viability.

As discussed earlier, the positive predictive value of CTG patterns during labour is very low. However, improved understanding of how different aspects of changes in fetal heart rate relate to fetal condition might improve fetal surveillance. During uncomplicated labour, intermittent hypoxaemia during contractions occurs and, as a result, essentially all fetuses show decelerations in heart rate during contractions. These decelerations are due to the vagally mediated chemoreflex in response to a fall in systemic oxygen tension. Healthy fetuses can compensate remarkably well for frequent decelerations before the development of profound acidosis and hypotension. The adaptive ability of the term fetus is illustrated by the finding that neonatal complications are extremely uncommon below a BD in umbilical cord arterial blood of 12 mmol/L[24]. Sheep experiments suggest that the inter-occlusion fetal heart rate might help to distinguish the state of fetal compensation. Prolonged deceleration in heart rate or overshoot tachycardia after the contraction or changes in inter-occlusion HRV are associated with developing fetal acidosis or hypotension[25]. The “vagal chemoreflex”, which mediates the first minute of the deceleration, is a sign of fetal adaptation to transient hypoxaemia during contractions. If decelerations are short, a healthy fetus can fully maintain normal oxygen delivery to vital organs virtually indefinitely. As the fetus severely deteriorates, a rising baseline, a loss of baseline variability and brief overshoot immediately after the deceleration develop[25]. Therefore, we suggest that it might be interesting to study spectral estimates

of fetal HRV in between contractions. Short segments of beat-to-beat heart rate can be used for this purpose. Since the lowest frequency we are interested in is 0.04 Hz, the beat-to-beat heart rate segment should be preferably 64 seconds when a Fourier transform is used. This seems short enough for measurement in between contractions. Probably the fetal heart rate pattern changes that reflect fetal hypotension and acidosis will be reflected in increased LFn power after the contraction due to increased sympathetic modulation. Spectral estimates of short segments of fetal HRV in between contractions might be better associated with fetal distress compared to longer segments containing contractions. This seems to be interesting for further research.

Fetal growth restriction

Fetal growth restriction due to placental dysfunction has important short and long term impacts that may reach into adulthood. Chronic hypoxia causes fetal growth restriction because of the restricted oxygen supply to somatic tissues. The optimal timing of delivery in pregnancies complicated by intrauterine growth restriction is still unresolved. The risks of prematurity have to be balanced against the risks of prolonged fetal exposure to hypoxaemia and acidaemia, possibly resulting in fetal damage or death. This decision is usually made based on a combination of CTG and umbilical artery Doppler ultrasound findings. Characteristic changes in fetal heart rate patterns associated with growth restriction include a reduction in fetal HRV and in accelerations[26]. These reductions are expected to be also reflected in spectral estimates of HRV. Future studies should focus on growth retarded fetuses and determine whether spectral estimates of HRV are useful in making treatment decisions in this vulnerable subgroup.

Sheep studies showed that the compensatory response to chronic hypoxia due to placental insufficiency involves a sympathetically mediated increased release of circulating catecholamines, redistribution of blood flow, resetting of the baroreceptor reflex, chronic hypertension and myocardial hypertrophy[27]. In addition, chronic hypoxia is associated with increased β-adrenoceptor sensitivity[28]. This increased sensitivity is expected to be reflected in spectral estimates of fetal HRV. Breborowicz et al. showed that spectral estimates of fetal HRV differ significantly between growth restricted fetuses and healthy control fetuses[12]. During quiescence, relative spectral density at the low frequencies is higher in growth restricted fetuses than in the control group[12]. During activity the relative spectral density in the LF range was higher in control fetuses than in growth restricted fetuses[12]. While in healthy fetuses striking differences were seen in LF spectral estimates between different behavioural states, in growth restricted fetuses these differences were diminished[12]. This difference suggests diminished LF reactivity of cardiac control in growth restricted fetuses. Vinkesteijn et al. found a decreased HRV in growth restricted fetuses which seemed to be due to altered sympathovagal balance[29]. They showed that LF/HF ratio of HRV was lower in premature growth restricted fetuses compared to control fetuses[29]. However, they did not correct for fetal movements, which are associated with increased power in the LF range[11]. Fetal movements are reduced in growth restricted fetuses and the autonomic response to fetal movements is decreased in growth restriction[12]. Therefore, the results observed by Vinkesteijn et al. might be due to differences in frequency of fetal movements or autonomic response to fetal movements.

In addition, they studied recordings of 18 to 49 seconds and thus some recordings will be too short for reliable interpretation of the LF range.

Intrauterine growth restriction is a common condition and an important cause of perinatal mortality[30]. Despite its importance and relatively high prevalence, the detection is poor[31]. For further research it would be interesting to study whether spectral estimates of fetal HRV can be used as a screening method to detect growth restricted fetuses in an early stage.

Epidemiologic evidence exists that small birthweight is a major predictor of risk for the development of arterial hypertension and death from coronary artery disease in adult life[32,33]. Substandard conditions during the critical period of intrauterine development may lead to fetal-programming and may produce adaptive changes in fetal anatomy, physiology and metabolism that have long term consequences. This theory is known as the "fetal origin of adult disease" or "Barker hypothesis". It has been suggested that increased sympathetic nervous system activity in utero is the underlying physiological mechanism for the relation between low birthweight and insulin resistance and increased blood pressure in adult life[34]. However, the underlying mechanisms for this dysfunction in autonomic regulation are not fully understood and as a result cannot be treated. Probably, spectral estimates of antepartum HRV may contribute to understanding these mechanisms.

Fetal ECG

In addition to beat-to-beat fetal heart rate extraction, abdominal measurement of the fetal ECG has the potential to determine the fetal vectorcardiogram. This fetal vectorcardiogram can be used to derive the standardised Einthoven ECG leads of the fetus[35]. This might be extremely valuable for fetal cardiology, e.g. for diagnosis and evaluation of fetal cardiac arrhythmia or for detection of congenital heart disease. Furthermore, we might speculate that multi-lead fetal ECG detection makes non-invasive ST-waveform analysis of the fetal ECG possible. Contrary to the current STAN® method, which uses only one scalp ECG lead, multi-lead fetal ECG probably provides more information on fetal condition since the standard Einthoven leads can be reconstructed. This might enable, antepartum ST analysis in high risk pregnancies, e.g. in case of fetal growth restriction. Since it is reported that ST-waveform analysis can also be used in fetuses of 30 to 36 weeks of gestational age[36], antepartum non-invasive ST-waveform analysis might be useful in premature fetuses.

In addition, measuring the fetal vectorcardiogram in time enables fetal movement detection[35]. Non-invasive fetal ECG, spectral estimates of HRV, heart rate and movement information might be useful for long term home monitoring of high risk patients. This seems of additional value for intrauterine growth restricted fetuses and fetuses of women with diabetes. Probably, fetal distress can be detected in an early stage although this has to be substantiated in future research. Home monitoring is expected to be highly cost-effective since hospitalisation is avoided and it is likely to increase quality of life of the pregnant women. Furthermore, non-invasive fetal ECG measurement is entirely free

of risks and causes little discomfort. In contrast to the conventional Doppler recording of fetal heart rate, prolonged recordings can be made without adjustments in electrode position.

References

1. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220-222.
2. Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93:1043-1065.
3. Siira SM, Ojala TH, Vahlberg TJ, Jalonen JO, Valimaki IA, Rosen KG, Ekholm EM. Marked fetal acidosis and specific changes in power spectrum analysis of fetal heart rate variability recorded during the last hour of labour. BJOG 2005;112:418-423.
4. Suzuki T, Kimura Y, Murotsuki J, Murakami T, Uehara S, Okamura K. Detection of a biorhythm of human fetal autonomic nervous activity by a power spectral analysis. Am J Obstet Gynecol 2001;185:1247-1252.
5. Chung DY, Sim YB, Park KT, Yi SH, Shin JC, Kim SP. Spectral analysis of fetal heart rate variability as a predictor of intrapartum fetal distress. Int J Gynaecol Obstet 2001;73:109-116.
6. Ohta T, Okamura K, Kimura Y, Suzuki T, Watanabe T, Yasui T, Yaegashi N, Yajima A. Alteration in the low-frequency domain in power spectral analysis of fetal heart beat fluctuations. Fetal Diagn Ther 1999;14:92-97.
7. Rantonen T, Ekholm E, Siira S, Metsala T, Leino R, Ekblad U, Välimäki I. Periodic spectral components of fetal heart rate variability reflect the changes in cord arterial base deficit values: a preliminary report. Early Hum Dev 2001;60:233-238.
8. Assali NS, Brinkman CR, Woods JR, Dandavino A, Nuwayhid B. Development of neurohumoral control of fetal, neonatal, and adult cardiovascular functions. Am J Obstet Gynecol 1977;129: 748-759.
9. van Geijn HP, Jongsma HW, de Haan J, Eskes TK. Analysis of heart rate and beat-to-beat variability: Interval difference index. Am J Obstet Gynecol 1980;138:246-252.
10. van Leeuwen P, Geue D, Lange S, Hatzmann W, Gronemeyer D. Changes in the frequency power spectrum of fetal heart rate in the course of pregnancy. Prenat Diagn 2003;23:909-916.
11. David M, Hirsch M, Karin J, Toledo E, Akselrod S. An estimate of fetal autonomic state by time-frequency analysis of fetal heart rate variability. J Appl Physiol 2007;102:1057-1064.
12. Breborowicz G, Moczko J, Gadzinowski J. Quantification of the fetal heart rate variability by spectral analysis in growth-retarded fetuses. Gynecol Obstet Invest 1988;25:186-191.
13. Spencer JA. Behavioral states and the peripartum period. Semin Perinatol 1992;16:217-222.
14. Dawes GS, Moulden M, Redman CW. System 8000: computerized antenatal FHR analysis. J Perinat Med 1991;19:47-51.
15. van Laar JO, Peters CH, Vullings R, Houterman S, Bergmans JW, Oei SG. Fetal autonomic response to severe acidaemia during labour. BJOG 2010;117:429-437.
16. van Laar JO, Peters CH, Houterman S, Wijn PF, Kwee A, Oei SG. Normalized spectral power of fetal heart rate variability is associated with fetal scalp blood pH. Early Hum Dev 2011;87:259-263.
17. Peters C, Vullings R, Bergmans J, Oei G, Wijn P. The effect of artifact correction on spectral estimates of heart rate variability. Conf Proc IEEE Eng Med Biol Soc 2008:2669-2672.
18. Peters CH, Vullings R, Rooijakkers MJ, Bergmans JW, Oei SG, Wijn PF. A continuous wavelet transform-based method for time-frequency analysis of artefact-corrected heart rate variability data. Physiol Meas 2011;32:1517-1527.

19. Low JA, Panagiotopoulos C, Derrick EJ. Newborn complications after intrapartum asphyxia with metabolic acidosis in the term fetus. Am J Obstet Gynecol 1994;170:1081-1087.
20. Heinis AM, Spaanderman ME, Gunnewiek JM, Lotgering FK. Scalp blood lactate for intra-partum assessment of fetal metabolic acidosis. Acta Obstet Gynecol Scand 2011;90:1107-1114.
21. Siira S, Ojala T, Ekholm E, Vahlberg T, Blad S, Rosen KG. Change in heart rate variability in relation to a significant ST-event associates with newborn metabolic acidosis. BJOG 2007;114:819-823.
22. Callaghan WM, MacDorman MF, Rasmussen SA, Qin C, Lackritz EM. The contribution of preterm birth to infant mortality rates in the United States. Pediatrics 2006;118:1566-1573.
23. Gaudier FL, Goldenberg RL, Nelson KG, Peralta-Carcelen M, Johnson SE, DuBard MB, Roth TY, Hauth JC. Acid-base status at birth and subsequent neurosensory impairment in surviving 500 to 1000 gm infants. Am J Obstet Gynecol 1994;170:48-53.
24. Low JA, Lindsay BG, Derrick EJ. Threshold of metabolic acidosis associated with newborn complications. Am J Obstet Gynecol 1997;177:1391-1394.
25. Westgate JA, Wibbens B, Bennet L, Wassink G, Parer JT, Gunn AJ. The intrapartum deceleration in center stage: a physiologic approach to the interpretation of fetal heart rate changes in labor. Am J Obstet Gynecol 2007;197:236.e1-11.
26. Henson G, Dawes GS, Redman CW. Characterization of the reduced heart rate variation in growth-retarded fetuses. Br J Obstet Gynaecol 1984;91:751-755.
27. Murotsuki J, Challis JR, Han VK, Fraher LJ, Gagnon R. Chronic fetal placental embolization and hypoxemia cause hypertension and myocardial hypertrophy in fetal sheep. Am J Physiol 1997;272: R201-R207.
28. Lindgren I, Altimiras J. Chronic prenatal hypoxia sensitizes beta-adrenoceptors in the embryonic heart but causes postnatal desensitization. Am J Physiol Regul Integr Comp Physiol 2009;297:R258-R264.
29. Vinkesteijn AS, Struijk PC, Ursem NT, Hop WC, Wladimiroff JW. Fetal heart rate and umbilical artery flow velocity variability in intrauterine growth restriction: a matched controlled study. Ultrasound Obstet Gynecol 2004;23:461-465.
30. Witter FR. Perinatal mortality and intrauterine growth retardation. Curr Opin Obstet Gynecol 1993;5:56-59.
31. Gardosi J. Clinical strategies for improving the detection of fetal growth restriction. Clin Perinatol 2011;38:21-31.
32. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ 1989;298:564-567.
33. Barker DJ, Osmond C, Kajantie E, Eriksson JG. Growth and chronic disease: findings in the Helsinki Birth Cohort. Ann Hum Biol 2009;36:445-458.
34. Phillips DI, Barker DJ. Association between low birthweight and high resting pulse in adult life: is the sympathetic nervous system involved in programming the insulin resistance syndrome? Diabet Med 1997;14:673-677.
35. Vullings R. Non-invasive fetal electrocardiogram: analysis and interpretation. PhD Thesis, Eindhoven University of Technology, Eindhoven, 2010.
36. Janků P, Hruban L, Kurecová B, Roztocil A, Kachlík P, Zahradnícková J. ST analysis of fetal ECG in premature deliveries during 30th-36th week of pregnancy. Ceska Gynekol 2006;71:163-168.

Addendum

Nederlandse samenvatting
List of abbreviations
List of publications
Dankwoord
Curriculum vitae

Nederlandse samenvatting

Tijdige herkenning van foetale nood, tijdens de zwangerschap en de bevalling, is van groot belang om neonatale morbiditeit en mortaliteit te voorkomen. Zoals beschreven in **hoofdstuk 1**, is het cardiotocogram een zinvolle screeningstest voor foetale bewaking. Echter, vanwege de beperkte specificiteit zijn aanvullende diagnostische testen nodig bij verdenking op foetale nood om onnodige kunstverlossingen te voorkomen. Potentiële aanvullende technieken, die gebruikt worden in de klinische praktijk, zijn microbloedonderzoek en ST-golfvorm analyse van het foetale elektrocardiogram (STAN®). Onderzoeken laten echter niet zien dat het gebruik van deze technieken leidt tot een reductie van het aantal keizersneden. Bovendien zijn deze technieken invasief en kunnen dus alleen gebruikt worden tijdens de baring gedurende de à terme periode. Het is van groot belang dat aanvullende methoden ontwikkeld worden die bijdragen aan een betrouwbaardere beoordeling van de foetale conditie. Bij voorkeur wordt de aanvullende informatie niet-invasief verkregen zodat de methode ook antepartum en voor bewaking van de premature foetus gebruikt kan worden.

Aanvullende informatie over de foetale conditie kan worden verkregen door middel van spectraal analyse van de foetale hartslagfrequentie variabiliteit. De foetale hartslag fluctueert onder invloed van het autonome deel van het centrale zenuwstelsel. Deze autonome modulatie van het hart wordt beschreven in **hoofdstuk 2**. Het sympathische en het parasympathische zenuwstelsel werken op deels verschillende tijdschalen. Frequentie analyse (spectraal analyse) van de foetale hartslagfrequentie variabiliteit kan zo de sympathische en parasympathische modulatie van het hart kwantificeren. De laagfrequente component van de hartslagfrequentie variabiliteit is geassocieerd met zowel sympathische als parasympathische modulatie, terwijl de hoogfrequente component alleen is geassocieerd met de parasympathische modulatie. Spectraalwaarden van de hartslagfrequentie variabiliteit geven dus indirect informatie over de foetale conditie en vergroten het inzicht in de foetale autonome respons van het hart. In **hoofdstuk 3**, worden de technische details voor het verkrijgen van de foetale hartslagfrequentie en de spectraalwaarden verstrekt.

In dit proefschrift wordt spectraal analyse van de foetale hartslagfrequentie variabiliteit onderzocht. De eerste doelstelling is om de waarde van spectraal analyse te bestuderen, als een instrument om de foetale conditie te bewaken tijdens de bevalling rond de à terme periode. De tweede doelstelling is om de spectraalwaarden niet-invasief te vervolgen tijdens de zwangerschap, om inzicht te verkrijgen in de ontwikkeling van de autonome modulatie van het foetale hart.

Sinds Akselrod de relatie beschreef tussen autonoom zenuwstelsel modulatie en laagfrequente en hoogfrequente pieken in frequentie domein wordt spectraal analyse van de hartslagfrequentie variabiliteit op grote schaal toegepast. Voor volwassen mensen zijn standaarden ontwikkeld voor hartslagfrequentie variabiliteit metingen en de fysiologische interpretatie hiervan. Hoewel hartslagfrequentie variabiliteit parameters van grote prognostische waarde zijn bij volwassen mensen in het geval van hart- en vaatziekten, is

weinig onderzoek gedaan naar de waarde van deze parameters bij de beoordeling van de foetale conditie, zoals beschreven in **hoofdstuk 4**. In dit hoofdstuk wordt de bestaande literatuur over spectraal analyse van de foetale hartslagfrequentie variabiliteit bij de mens beoordeeld om de waarde van spectraal analyse voor foetale bewaking te bepalen. Artikelen die spectraal analyse van de foetale hartslagfrequentie variabiliteit bij de mens beschreven en de spectrale energie vergeleken met foetale bloedgas waarden werden opgenomen. Slechts zes studies voldeden aan onze inclusiecriteria. Eén studie vond een initiële stijging van de laagfrequente energie tijdens de eerste fase van achteruitgang van de foetale conditie. Deze stijging werd toegeschreven aan stress geïnduceerde sympathische overactiviteit. Vijf van de zes studies toonden een daling van de laagfrequente energie in geval van foetale nood. Deze daling van de laagfrequente energie in geval van ernstige foetale nood werd toegeschreven aan immaturiteit of decompensatie van het foetale autonome zenuwstelsel. Deze bevindingen ondersteunen de hypothese dat spectraal analyse van foetale hartslagfrequentie variabiliteit een veelbelovende methode voor foetale bewaking is.

Alle studies opgenomen in het overzichtsartikel beschreven in hoofdstuk 4, gebruikten absolute waarden van laag- en hoogfrequente energie. Hoewel de absolute laag- en hoogfrequente energie van de foetale hartslagfrequentie variabiliteit nuttige informatie geven over autonome modulatie, met name bij het bestuderen van autonome ontwikkeling, kan laag- en hoogfrequente energie ook worden gemeten in genormaliseerde eenheden. Genormaliseerde laag- en hoogfrequente energie vertegenwoordigen de relatieve waarde van elke component in verhouding tot de totale spectrale energie. Adrenerge stimulatie kan leiden tot een sympathisch gemoduleerde verhoging van de hartslagfrequentie van de foetus. Er bestaat echter een negatieve correlatie tussen de hartslagfrequentie en de hartslagfrequentie variabiliteit. Hierdoor kan sympathische stimulatie de totale energie van de hartslagfrequentie variabiliteit verminderen en zo ook de absolute laagfrequente energie beïnvloeden. Bij normaliseren van de absolute laag- en hoogfrequente energie ten opzichte van de totale energie kan een verschuiving in de activiteit van hoogfrequent naar laagfrequent zichtbaar worden, zodat de verwachte onderliggende sympathische activiteit naar voren komt. Dus doordat veranderingen in totale energie absolute spectraalwaarden in dezelfde richting beïnvloeden, lijkt het gebruik van genormaliseerde waarden van laag- en hoogfrequente energie meer geschikt voor foetale bewaking. Met andere woorden, genormaliseerde spectraalwaarden detecteren relatieve veranderingen die niet worden gemaskeerd door veranderingen in de totale energie. Genormaliseerde laag- en hoogfrequente energie worden berekend door de laagfrequente en de hoogfrequente energie te delen door de totale energie. Deze genormaliseerde laag- en hoogfrequente energie vertegenwoordigen de evenwichtige modulatie van de twee takken van het autonome zenuwstelsel. In **hoofdstuk 5** hebben we verondersteld dat de autonome cardiale controle functioneel is in de à terme foetus en de hypothese getoetst dat de genormaliseerde laagfrequente energie stijgt in geval van foetale nood, als gevolg van toegenomen sympathische modulatie. Tijdens de baring, gedurende de à terme periode, werden tien acidotische foetussen vergeleken met tien gezonde foetussen. Gedurende de laatste 30 minuten van de baring hadden acidotische foetussen significant hogere genormaliseerde laagfrequente en lagere genormaliseerde hoogfrequente energie

dan gezonde foetussen. Dit wijst op toegenomen sympathische modulatie. Er waren geen verschillen in absolute laag- of hoogfrequente energie tussen beide groepen. De verschillen in genormaliseerde spectraalwaarden van de hartslagfrequentie variabiliteit werden niet in een eerder stadium van de bevalling waargenomen. Concluderend lijkt het erop dat het autonome zenuwstelsel van de menselijke foetus gedurende de à terme periode adequaat reageert op ernstige stress tijdens de bevalling. De genormaliseerde spectraalwaarden van de hartslagfrequentie variabiliteit lijken onderscheid te kunnen maken tussen een normale en abnormale conditie van de foetus.

Hoewel we significante verschillen vonden in de genormaliseerde spectraalwaarden tussen gezonde en acidotische foetussen, vroegen we ons af of de spectrale energie van de hartslagfrequentie variabiliteit ook gerelateerd is aan foetale nood in een eerder stadium. De volgende stap, in **hoofdstuk 6**, was dan ook, om te onderzoeken of spectraalwaarden zijn gerelateerd aan microbloedonderzoek pH van de foetus tijdens de bevalling. A terme foetussen, in schedelligging, die een of meer microbloedonderzoeken ondergingen tijdens de baring, werden bestudeerd. De foetale hartslagfrequentie segmenten voorafgaand aan het microbloedonderzoek, werden gebruikt om de spectraalwaarden te berekenen. In totaal werden 39 microbloedonderzoeken van 30 foetussen bestudeerd. De resultaten toonden dat de genormaliseerde spectraalwaarden zijn gerelateerd aan de foetale microbloedonderzoek pH, terwijl absolute spectraalwaarden niet zijn gerelateerd aan de foetale pH. Verder werd aangetoond dat de genormaliseerde laagfrequente energie negatief is gerelateerd en dat de genormaliseerde hoogfrequente energie positief is gerelateerd aan de foetale pH. Deze bevindingen wijzen op toegenomen sympathische en afgenomen parasympathische modulatie van het hart als de foetale pH daalt. Deze studie bevestigt de hypothese dat genormaliseerde spectraalwaarden van de foetale hartslagfrequentie variabiliteit gerelateerd zijn aan foetale nood in een vroeg stadium.

Studies hebben aangetoond dat absolute laag- en hoogfrequente energie toenemen naarmate de zwangerschapsduur vordert, hetgeen wordt toegeschreven aan rijping van het autonome zenuwstelsel van de foetus. Aangezien het nog onduidelijk is of genormaliseerde laag- en hoogfrequente energie veranderen in het verloop van de zwangerschap, moet voordat spectraal analyse kan worden gebruikt voor foetale bewaking, worden vastgesteld of gecorrigeerd moet worden voor zwangerschapsduur. Bovendien worden fluctuaties van het foetale autonome zenuwstelsel, en dus spectraalwaarden van de foetale hartslagfrequentie variabiliteit, rond de à terme periode beïnvloed door de foetale gedragstoestand. Aangezien deze gedragstoestanden continueren tijdens de bevalling, is diepgaand inzicht in de wijze waarop de gedragstoestanden de spectraalwaarden beïnvloeden noodzakelijk voor de interpretatie van spectraalwaarden tijdens de bevalling. Daarom werd in **hoofdstuk 7** onderzocht of er verschillen in spectraalwaarden bestaan tussen gezonde randpremature en serotiene foetussen tijdens de bevalling. Indien dergelijke verschillen bestaan, moet hiermee rekening worden gehouden voor het gebruik van spectraal analyse voor foetale bewaking. Tevens werden de non-rapid eye movement (REM) en de REM slaap stadia afzonderlijk bestudeerd om de invloed van de foetale gedragstoestanden op de spectraalwaarden van de foetale hartslagfrequentie variabiliteit tijdens de bevalling te bepalen. Er werden geen significante verschillen in

spectraalwaarden gevonden tussen de randpremature en de serotiene foetussen tijdens de REM slaap. Tijdens de non-REM slaap was de genormaliseerde laagfrequente energie lager en waren de absolute en de genormaliseerde hoogfrequente energie hoger in de serotiene, ten opzichte van de randpremature foetussen. Er werden geen significante verschillen in absolute laagfrequente energie waargenomen tussen beide groepen. Absolute laag- en hoogfrequente energie en genormaliseerde laagfrequente energie waren hoger en de genormaliseerde hoogfrequente energie was lager tijdens REM slaap, vergeleken met de non-REM slaap in beide groepen. Dit is waarschijnlijk een teken van sympathische dominantie tijdens de REM slaap toestand bij de foetus rond de à terme periode. Daarnaast lijkt bij de serotiene foetus de parasympathische modulatie tijdens de non-REM slaap hoger te zijn vergeleken met de randpremature foetus. Concluderend, de foetale gedragstoestand en de zwangerschapsduur leiden tot een aanzienlijke variatie in spectraalwaarden bij de foetus tijdens de bevalling, rond de à terme periode. Hiermee moet men rekening houden voordat spectraalwaarden gebruikt kunnen worden voor foetale bewaking.

In de hoofdstukken 4 tot en met 6 werden spectraalwaarden van de foetale hartslag-frequentie variabiliteit bestudeerd met behulp van foetale elektrocardiogram metingen verkregen door middel van een schedelelektrode tijdens de bevalling. Echter, de tweede doelstelling van dit proefschrift is om spectraalwaarden niet-invasief te verkrijgen tijdens de zwangerschap om inzicht te krijgen in de ontwikkeling van de autonome modulatie van het foetale hart. Het foetale elektrocardiogram is ook aanwezig op het maternale abdomen, maar is dan veel kleiner in amplitude en wordt verstoord door het maternale elektrocardiogram en door ruis. **Hoofdstuk 8** richt zich op de niet-invasieve meting van het foetale elektrocardiogram via de buik van de moeder. Deze metingen maken het mogelijk om de foetale hartslagfrequentie niet-invasief te verkrijgen. Daarom kan deze methode worden gebruikt om de spectraalwaarden van de foetale hartslagfrequentie variabiliteit te verkrijgen tijdens de zwangerschap. Abdominale meting van het foetale elektrocardiogram geeft waardevolle aanvullende informatie maar wordt gehinderd door een slechte signaal-ruis-verhouding in bepaalde delen van de zwangerschap, bijvoorbeeld tijdens de preterme periode en tijdens de vernix caseosa periode. Om de bruikbaarheid van abdominale foetale elektrocardiogram metingen te vergroten, werd een algoritme ontwikkeld dat gebruik maakt van à priori kennis over de fysiologie van het foetale hart om de foetale elektrocardiogram componenten te versterken voor QRS-detectie. Evaluatie van deze methode, op gegenereerde foetale elektrocardiogram metingen met gecontroleerde signaal-ruis-verhouding, toonde uitstekende resultaten.

De methode voor niet-invasieve foetale elektrocardiogram en hartslagfrequentie detectie, gepresenteerd in hoofdstuk 8, is gebruikt voor de analyse in **hoofdstuk 9**. De haalbaarheid van deze methode in een longitudinale patiënten studie werd onderzocht. Bovendien werden veranderingen in spectraalwaarden van de foetale hartslagfrequentie variabiliteit gedurende de zwangerschap onderzocht en gerelateerd aan foetale gedragstoestanden om de ontwikkeling van de autonome modulatie van het foetale hart te bestuderen. De resultaten toonden aan dat ongeveer 3%, van de niet-invasieve foetale elektrocardiogram metingen, kan worden gebruikt voor spectraal analyse.

Verbetering van de algoritmen is nodig om meer data van goede kwaliteit te verkrijgen. Het percentage succesvol verkregen gegevens is afhankelijk van de zwangerschapsduur. Vóór 18 en tussen 30 en 34 weken konden geen foetale hartslagfrequentie gegevens van goede kwaliteit verkregen worden. Resultaten toonden een toename van de laag- en hoogfrequente energie van de foetale hartslagfrequentie variabiliteit tussen 21 en 30 weken zwangerschapsduur. Deze stijging in laag- en hoogfrequente energie is waarschijnlijk het gevolg van toegenomen sympathische en parasympathische modulatie en is wellicht een teken van autonome ontwikkeling. Bovendien werd aangetoond dat het sympathische zenuwstelsel dominant is tijdens de REM slaap vergeleken met de non-REM slaap bij foetussen van 34 tot 41 weken zwangerschapsduur. Deze resultaten zijn vergelijkbaar met de resultaten tijdens de bevalling rond de à terme periode. Gedurende de periode van 34 tot 41 weken van de zwangerschap werd een (niet-significante) afname van de absolute en genormaliseerde laagfrequente energie en een (niet-significante) toename van de absolute en genormaliseerde hoogfrequente energie waargenomen. Deze niet significante veranderingen in de spectraalwaarden bij foetussen rond de à terme periode worden geassocieerd met veranderingen in de foetale gedragstoestand en toegenomen parasympathische modulatie als de zwangerschap vordert. Aanvullend onderzoek is nodig om dit te bevestigen.

List of abbreviations

ANS	Autonomic Nervous System
AV	Atrioventricular
BD	Base Deficit
BPM	Beats Per Minute
CTG	Cardiotocogram
DC	Direct Current
ECG	Electrocardiogram
EFM	Electronic Fetal Monitoring
FBS	Fetal Scalp Blood Sampling
FFT	Fast Fourier Transform
FHR	Fetal Heart Rate
GA	Gestational Age
GEE	Generalised Estimating Equations
HF	High Frequency
HFn	Normalised High Frequency
HRV	Heart Rate Variability
IUGR	Intrauterine Growth Restriction
LF	Low Frequency
LF/HF	Low Frequency to High Frequency Ratio
LFn	Normalised Low Frequency
LR	Likelihood Ratio
LTV	Long Term Variation
NEMO	Non-invasive Electrophysiologic Monitor for Obstetrics
PSD	Power Spectral Density
REM	Rapid Eye Movement
RR	Relative Risk
RSA	Respiratory Sinus Arrhythmia
SA	Sinoatrial
SD	Standard Deviation
SNR	Signal-to-Noise Ratio
STAN®	ST-waveform Analysis
STV	Short Term Variation
TF	Total Frequency
VCG	Vectorcardiogram
VLF	Very Low Frequency
WT	Wavelet Transform

List of publications

Journal Papers

1. Rabotti C, Mischi M, **van Laar JO**, Aelen P, Oei SG, Bergmans JW. Relationship between electrohysterogram and internal uterine pressure: a preliminary study. Conf Proc IEEE Eng Med Biol Soc 2006;1:1661-1664.
2. Roovers JP, **van Laar JO**, Loffeld C, Bremer GL, Mol BW, Bongers MY. Does urodynamic investigation improve outcome in patients undergoing prolapse surgery? Neurourol Urodyn 2007;26:170-175.
3. Rabotti C, Mischi M, **van Laar JO**, Oei SG, Bergmans JW. Electrohysterographic analysis of uterine contraction propagation with labor progression: a preliminary study. Conf Proc IEEE Eng Med Biol Soc 2007;1:4135-4138.
4. **van Laar JO,** Porath MM, Peters CH, Oei SG. Spectral analysis of fetal heart rate variability for fetal surveillance: review of the literature. Acta Obstet Gynecol Scand 2008;87:300-306.
5. Rabotti C, Mischi M, **van Laar JO**, Oei SG, Bergmans JW. Estimation of internal uterine pressure by joint amplitude and frequency analysis of electrohysterographic signals. Physiol Meas 2008;29:829-841.
6. Rabotti C, Mischi M, **van Laar JO**, Oei SG, Bergmans JW. On the propagation analysis of electrohysterographic signals. Conf Proc IEEE Eng Med Biol Soc 2008;1:3868-3871.
7. **van Laar JO**, Peters CH, Vullings R, Houterman S, Oei SG. Power spectrum analysis of fetal heart rate variability at near term and post term gestation during active sleep and quiet sleep. Early Hum Dev 2009;85:795-798.
8. Rabotti C, Mischi M, **van Laar JO**, Oei SG, Bergmans JW. Inter-electrode delay estimators for electrohysterographic propagation analysis. Physiol Meas 2009;30:745-761.
9. Rabotti C, Mischi M, **van Laar JO**, Oei SG, Bergmans JW. Myometrium electromechanical modeling for internal uterine pressure estimation by electrohysterography. Conf Proc IEEE Eng Med Biol Soc 2009;1:6259-6262.
10. Vinken MP, Rabotti C, Mischi M, **van Laar JO**, Oei SG. Nifedipine-induced changes in the electrohysterogram of preterm contractions: feasibility in clinical practice. Obstet Gynecol Int 2010.
11. **van Laar JO**, Peters CH, Vullings R, Houterman S, Bergmans JW, Oei SG. Fetal autonomic response to severe acidaemia during labour. BJOG 2010;117:429-437.
12. **van Laar JO**, Peters CH, Houterman S, Wijn PF, Kwee A, Oei SG. Normalized spectral power of fetal heart rate variability is associated with scalp blood pH. Early Hum Dev 2011;87:259-263.
13. Peters CH, **van Laar JO**, Vullings R, Oei SG, Wijn PF. Beat-to-beat heart rate detection in multi-lead abdominal fetal ECG recordings. Med Eng Phys 2012;34:333-338.
14. Beulen L, **van Laar JO**, Oei SG. The use of PR interval - fetal heart rate correlation analysis in intrapartum fetal monitoring: a systematic review of the literature. Submitted for publication.

15. **van Laar JO**, Warmerdam GJ, Vullings R, Peters CH, Houterman S, Wijn PF, Andriessen P, van Pul C, Oei SG. Fetal heart rate variability in frequency-domain during pregnancy, obtained from non-invasive electrocardiogram recordings. Submitted for publication.

International conference presentations

1. Vullings R, Peters CH, **van Laar JO**, Wijn PF, Oei SG. Fetal heart rate and sympathetic activity determined non-invasively from the maternal abdomen. World Congress of Perinatal Medicine, Zagreb, 21-24 September 2005.
2. **van Laar JO**, Prudon MJ, Vullings R, Peters CH, Wijn PF, Oei SG. Spectral analysis can discriminate between normal fetal condition and fetal acidosis. World Congress of Perinatal Medicine, Florence, 9-13 September 2007.
3. **van Laar JO**, Peters CH, Vullings R, Oei SG. Increased parasympathetic activity during rest in post term fetuses. European Congress of Perinatal Medicine, Istanbul, 10-13 September 2008.
4. **van Laar JO**, Bolderdijk AM, Peters CH, Oei SG. Fetal sympathetic modulation during the second trimester of pregnancy: preliminary results. Stipendium Perinatologie en Maternale Ziekten. Dutch Society of Perinatal Medicine Symposium, Utrecht, 28 November 2008.
5. **van Laar JO**, Peters CH, Houterman S, Wijn PF, Oei SG. Normalised spectral power of fetal heart rate variability predicts fetal scalp blood pH. World Congress of Perinatal Medicine, Berlin, 24-28 October 2009.

International conference posters

1. **van Laar JO**, Vullings R, Peters CH, Wijn PF, Oei SG. Customized spectral band analysis of fetal heart rate variability compared with conventional Fourier transform. 33rd annual meeting of the Fetal Neonatal Physiological Society, Cambridge, 17-20 September 2006.
2. **van Laar JO**, Vullings R, Peters CH, Wijn PF, Oei SG. The usefulness of spectral analysis for fetal monitoring; systematic review. 33rd annual meeting of the Fetal Neonatal Physiological Society, Cambridge, 17-20 September 2006.

Dankwoord

Dit proefschrift is het resultaat van samenwerking met vele mensen die ik graag wil bedanken. Allereerst een woord van dank aan alle vrouwen en hun ongeboren baby's die hebben deelgenomen aan mijn onderzoek. Daarnaast wil ik de volgende personen bedanken voor de bijdrage die ze hebben geleverd aan dit proefschrift:

Prof.dr. S.G. Oei, beste Guid, jij nam mij aan als arts-assistent gynaecologie in het MMC en introduceerde me al snel binnen de TOP-groep. Bedankt voor het vertrouwen in mij en alle kansen die je me gegeven hebt. De eerste sectio, de eerste uterus extirpatie, de eerste presentatie op een wereldcongres en de eerste publicatie, het was allemaal onder jouw begeleiding. En nu mag ik de eerste arts zijn die bij jou promoveert op de TU/e, wat een eer. Je bent een voorbeeld, wat jij allemaal onderneemt en voor elkaar krijgt is ongelooflijk en dat altijd met een grote glimlach op je gezicht! Dank voor alles wat jij voor mij hebt gedaan.

Prof.dr.ir. P.F.F. Wijn, beste Pieter, jij was vanaf het begin betrokken. Je gaf me veel vrijheid maar hielp met het uitzetten van de grote lijnen, haalde me zo nu en dan uit de put als ik was vastgelopen in technische details en wist altijd op de juiste momenten een slimme afstudeerstudent aan te nemen voor technische hulp. Bedankt!

Ir. R. Vullings, beste Rik, dank voor je begeleiding bij het laatste deel van dit proefschrift. Toen jij betrokken raakte ging alles een stuk sneller. Mijn promotie is een primeur voor jou als copromotor. Ik bewonder je kennis en intellectuele vermogen, je commentaar was altijd bijzonder nuttig.

Prof.dr.ir. J.W.M. Bergmans, prof.dr. J.G. Nijhuis, prof.dr. F.P.H.A. Vandenbussche, prof.dr. G.H.A. Visser en prof.dr.ir. A.C.P.M. Backx bedankt voor het beoordelen van mijn manuscript.

Caroline Hermans en Elize Sturkenboom-van de Wetering, mijn paranimfen. Lieve Caroline, jij bent al vanaf de basisschool mijn vriendin. We kennen elkaar door en door en hebben altijd alles samen gedeeld. Wat heb ik je gemist het afgelopen jaar, toen jij in Mozambique was. Lieve Elize, jouw gezin met Floris, Annelore en Amandine is als familie voor mij. Vrijwel elk vrij weekend weten we elkaar te vinden; heerlijk dat onze mannen en onze meisjes ook zulke goede vrienden zijn. Lieve meiden, jullie zijn mij ongelooflijk dierbaar, mijn maatjes door dik en dun, het was vanzelfsprekend om jullie te vragen mijn paranimfen te zijn!

Maatschap gynaecologie en verloskunde van het Máxima Medisch Centrum, wat hebben jullie het goed voor elkaar en wat zijn jullie een inspirerend team. Ik ben er trots op dat ik in het MMC ben opgeleid. Bedankt voor alles wat jullie mij hebben geleerd, jullie weten het beste in de AIOS naar boven te halen!

Collega arts-assistenten gynaecologie van het Máxima Medisch Centrum, wat is het altijd fijn werken met jullie in de kliniek. Lieve Josje en Femke, “mijn roomies”, we wisten elkaar altijd te vinden! Altijd vrolijke Femke, jij zag meteen dat tweede “smurf van Doorn” een jongen is! Josje, jij gaf het voorbeeld dat het allemaal kan; een goede AIOS zijn en promoveren. Bedankt voor het strikdiploma en alle “tips and tricks” over promoveren.

Verloskundigen, verpleegkundigen, kraamverzorgsters en secretaresses van het Máxima Medisch Centrum, jullie creëren zo’n fijne sfeer in het ziekenhuis dat je af en toe bijna vergeet dat je aan het werk bent. Jullie gaven mij altijd de ruimte om metingen te doen! Beste Cedric, dankzij jou zijn Emilie en Florian zonder al te veel “sympathische activiteit” geboren. Zelfs op je eigen vrijgezellendag stond je midden in de nacht voor ons klaar, het was heel fijn dat je er was!

Gynaecologen en arts-assistenten van het Maastricht Universitair Medisch Centrum, bedankt voor de leerzame tijd, voor jullie interesse in mijn onderzoek en voor de 3 maanden “schrijfstage” die jullie mij gunden om mijn proefschrift af te ronden. Collega AIOS, bedankt voor de (te?) gezellige tijd in onze enorme assistentenkamer! Lieve Rafli, Emilie en Esther, mijn carpoolmaatjes, met jullie was de reis naar Maastricht nooit saai!

Nicol Smeets, mijn onderzoeksmaatje. We hebben samen heel wat congressen bezocht. Zagreb, Florence, Istanbul, Berlijn het was altijd leerzaam maar ook super gezellig met jou! Jouw proefschrift is ook bijna af!

Dr. C.J.M. van Binsbergen en dr. C. Willekes mijn mentoren. Lieve Nelleke, wat ben ik blij dat jij mijn mentor was! Je stond me altijd bij met raad en daad en was er oprecht voor me als ik je nodig had. Lieve Christine, behalve mijn mentor was jij ook nog “mijn gynaecoloog” tijdens de zwangerschap van Emilie. Je geweldige kennis van prenatale diagnostiek werkt aanstekelijk. Het was telkens een feest om bij je op “controle” te komen. Ik zou zo graag nog veel meer van je leren.

Voormalige studenten: Anne Bolderdijk, Marc Prudon, Maartje Vinken, Lean Beulen en Hanke Schalks bedankt voor alle metingen die jullie gedaan hebben voor de longitudinale studie. Guy Warmerdam, wat was ik blij met jouw inzet voor de longitudinale studie! Dankzij jou, kon ik de data analyseren en gebruiken voor mijn proefschrift.

Klinisch fysici, dr.ir. C.H.L. Peters en dr.ir. C. van Pul, beste Chris en Carola, bedankt voor de technische ondersteuning. Beste Chris, jij was vanaf het begin tot het einde betrokken, bedankt voor het “dokter-proof” maken van het spectraal analyse programma. Ook bedankt voor alle vragen die je door de jaren heen beantwoord hebt, zonder jou was dit boekje er zeker niet geweest. Lieve Carola, bedankt voor al je hulp bij de longitudinale studie, het was heerlijk om met je samen te werken. Ik hoop dat onze samenwerking niet stopt na mijn promotie.

Medewerkers van de medische bibliotheek, Bart en Eugenie, jullie wisten altijd super snel alle benodigde boeken en artikelen tevoorschijn te toveren. Bedankt voor jullie hulp.

Epidemioloog, dr. S. Houterman, beste Saskia, mijn "Samantha" bedankt voor alle "tips and tricks" op het gebied van de statistiek. Je was altijd heel laagdrempelig bereikbaar (met een theetje). Wat jammer dat je niet meer in het MMC werkt.

Barbara Vermeulen, jij kreeg altijd alle vastgelopen programma's en apparaten weer snel aan de praat, TOP!

Dr. P. Andriessen, beste Peter, dank voor een kritische blik op hoofdstuk 2 en 9.

Henk Dinnissen, dank voor het ontwerpen van de lay-out van mijn proefschrift.

Angelique Lemmens, dank voor het maken van de prachtige foto's en voor het ontwerpen van de cover van mijn proefschrift.

Studie vriendinnen: lieve Eefke, Esther, Esther, Iris, Nieke, Nouchka, Marjolein, Marlies, Wendy en Renate bedankt voor de altijd gezellige feestjes en borrels. Lieve Bouke, Marlijn, Nicole en Tessa vanaf nu nog vaker "high tea". Lieve Rinske; we zien elkaar te weinig, maar het is altijd "lekker chillen" met de meiden en binnenkort ook met de jongens.

Schoonfamilie, lieve Frank & Elly, Muriel & Wouter, Lars & Sandra en Odin & Krista jullie oprechte interesse voor alles wat ik doe waardeer ik enorm.

Lieve Ron, mijn grote broer, jij hebt mij vroeger wereldwijs gemaakt, dankzij jou kan ik tegen een stootje. Bedankt ook voor alle heerlijke en gezellige etentjes samen met Irene en Guy.

Lieve papa en mama, jullie verdienen een ereplaats in dit dankwoord. Ik hoef maar te bellen en jullie komen mij helpen met wat dan ook. Bedankt voor jullie onvoorwaardelijke liefde en steun, mede namens Guy en Emilie. Het is fantastisch om te zien hoe jullie met ons kleine meisje omgaan. Ze vindt het heerlijk bij opa en oma op de "kinderboerderij" in Roosteren!

Mijn gezinnetje, lieve Guy, Emilie en Florian, samen met jullie voel ik me compleet. Lieve nuchtere Guy, mijn rots in de branding. Jij geeft me rust in ons soms hectische leven. Allerliefste Emilie, jij leerde mij relativeren. Jouw stralende lach, laat me alles om me heen vergeten. Lieve Florian, jouw getrappel in mijn buik was de beste motivatie om dit boekje vlot af te maken. Het is niet te beschrijven hoeveel ik van jullie hou!

Curriculum vitae

Judith van Laar werd geboren op 21 februari 1980 te Sittard. In 1998 haalde ze haar VWO diploma aan de Scholengemeenschap Sint Ursula te Horn. Hetzelfde jaar startte ze de geneeskunde opleiding aan de Radboud Universiteit Nijmegen. Na het behalen van haar artsexamen in 2004 werkte ze als arts-assistent obstetrie en gynaecologie in het Máxima Medisch Centrum te Veldhoven waar ze in 2006 startte met haar specialisatie tot gynaecoloog (opleiders prof.dr. S.G. Oei en dr. M.Y. Bongers). In deze periode werd gestart met fundamenteel perinatologisch onderzoek, onder begeleiding van prof.dr. S.G. Oei en in samenwerking met de Technische Universiteit Eindhoven, hetgeen de aanvang was van dit proefschrift. Het academische deel van de specialisatie werd in 2009 gestart in het Maastricht Universitair Medisch Centrum (opleiders prof.dr. G.G. Essed, prof. dr. R.F. Kruitwagen en dr. G.A. Dunselman). In 2012 keerde ze terug naar het Máxima Medisch Centrum te Veldhoven (opleiders dr. M.Y. Bongers en dr. C.A. Koks) voor de laatste fase van de opleiding.
Judith van Laar woont samen met Guy van Doorn. Samen hebben zij een dochter Emilie. De geboorte van hun tweede kind wordt verwacht rond de publicatie van dit proefschrift.