

STUDY OF HEART RATE VARIABILITY AS A MARKER OF ASPHYXIA/HYPOXIA.

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STUDY OF HEART RATE VARIABILITY AS A MARKER OF
ASPHYXIA/HYPOXIA.

by

Federico Cardona Rocha.

Declaration of Originality

A thesis submitted in fulfillment of the requirements for the degree of Doctor of Philosophy in the department of Engineering, University of Leicester, U.K.

This thesis is entirely my own original work unless otherwise acknowledged in the text or by references. No part of it has been submitted for any other degree, either to the University of Leicester or to any other University.

Signed :


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Date: 07-Jun-2011

Abstract

Study of Heart rate variability as a marker of asphyxia/hypoxia.

Federico Cardona Rocha.

The onset of labour represents the starting point of a perilous challenge in life, as a new born must adapt to an unknown environment. During this adaptation there are several risks: hypoxia, asphyxia, trauma, intervention and, in worst case scenario, death. These risks can be reduced through electronic fetal monitoring.

During this delicate period the study and analysis of the variability in beat-to-beat intervals of fetal heart rate plays a fundamental role in the pursuit of fetal wellbeing, reduction of fetal morbidity and mortality. Given that the use of an animal model allows direct experimental manipulation of the subjects and their environment and considering the ethical issues and difficulties to acquire data related to asphyxia during labour and delivery, linear techniques (time domain and frequency domain) and non-linear techniques (detrended fluctuation analysis, complexity analysis and Poincaré indices and plots) have been initially implemented for the study of heart rate variability (HRV) using data from the animal model. Data was acquired from experiments in which rats were submitted to controlled episodes of asphyxia (0, 1, 3, 5 and 7 min). Linear and non-linear methods highlighted significant differences in HRV before, during and after the insult. We show how, through a multiparametric analysis, it is possible to detect the onset of asphyxia. Furthermore, tracking the changes in heart rate variability along time, we suggest a novel non-invasive way to assess the amount of injury suffered.

With this background we applied HRV analysis to data collected during labour and delivery. We have obtained fetal beat-to-beat heart intervals from non-invasive Doppler ultrasound using Wavelet transform, Hilbert-Huang transform and Autocorrelation function, and these were compared with beat to beat heart intervals extracted from invasive scalp fetal ECG used as a gold standard. For the autocorrelation approach the results of HRV obtained from Doppler ultrasound, using both linear and non-linear analysis, correlate very well with those obtained using fetal scalp ECG. We also modelled and measured the recovery time (from nadir to baseline) following a deceleration of fetal heart rate to study the recovery behaviour and its relation with the development of hypoxic scenarios.

The results presented here provide a framework to detect and assess asphyxia by means of linear and non-linear techniques. These techniques have been tested first in an animal model and later in data collected during labour and delivery, showing that Doppler ultrasound provides a reliable alternative for assessing fetal heart rate variations non-invasively during pregnancy and delivery, when fetal scalp ECG is not available. Nevertheless more data needs to be collected and studied using the multiparametric HRV analysis described here to fully validate this approach.

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This Thesis is dedicated to the memory of

Federico Cardona Aguilar (1943-2008)

Mentor, best friend and father.

*We plan this journey together and was not the same without you, but I know that we will
catch up.*

Pascuala Rocha de Cardona (1948-1988)

Example of life, motivation and mother

Physically you weren't here but you always supported and encouraged me.

Alejandro Cardona Rosales (1915-2010)

Grandfather.

Role model and who had words of wisdom at all times.

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I accomplish this in part because you teach me how to multiply at your own way.

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List of publications

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Cardona Rocha, F., Cardona, A.R., Schlindwein, F.S. "A Non-invasive study of fetal heart rate variability during labour", 1st International Conference on Applied Mathematics, Toluca, Mexico, 4-6 November 2009.

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Cardona Rocha, F., Schlindwein, F.S., "Heart rate variability as a marker for asphyxia/hypoxia", 19th Biennial International Eurasip Conference BIOSIGNAL 2008, Brno Czech Republic, pp. 6-8, June 29- July 1, 2008.

Glossary of abbreviations and clinical terms.

In the interest of clarity and due to the fact this research work is cross-disciplinary, a glossary of clinical terms, technical and explanations of contextual descriptors are provided.

- Hypoxia: Is a pathological condition in which the body is deprived of proper oxygen supply.
- Cerebral palsy: Group of progressive conditions caused by brain damage before birth or during infancy.
- Encephalopathy: Disorder or disease of the brain, does not describe a single disease, describe a global brain dysfunction.
- Intrapartum: During labour or delivery
- Antepartum: Before labour and delivery.
- Postpartum: After labour and delivery.
- Bradycardia: Heart rate under the normal or expected value.
- Tachycardia: Heart rate that exceeds the normal range.
- PO₂: Pressure exerted by O₂ that is freely floating in plasma.
- PaO₂: Partial pressure of oxygen in arterial plasma.
- PaCO₂: Partial pressure of carbon dioxide in arterial plasma.
- bpm: beats per minute
- CTG: Cardiotocography, measurement of the fetal heart rate in combination with uterine contractions.
- EFM: electronic fetal monitoring.
- ECG: Electrocardiogram

Chapter 1

Introduction.

"There is no achievement without goals" Robert J. Mckaine

1.1 Historical Notes.

Not long ago the fetus was viewed not like a patient more like a passenger, it is surprising that although since the 17th century when Marsac a French physician was credited as the first having heard the fetal heart, many years passed by and nothing was done to improve fetal health inside the uterine 'black-box'. Then in 1812 auscultation was first described by Jean Alexander hearing the fetal heart beat through a wooden fetoscope. In 1833 Kennedy commented the relationship between cord compression and a slow return of fetal heart rate after bradycardia. By 1903 Williams postulated that "the rate of the fetal heart is subject to considerable variation which afford us a fairly reliable means of judging as to the wellbeing of the child as a general rule, its life should be considered in danger when the heartbeats fall below 100 or exceed 160" (Gibb and Arulkumaran, 1997). These early contributions marked the path to follow in the pursuit of fetal well-being through the monitoring of the fetal heart rate. Then from the first electronically observed fetal electrocardiogram by Cremer in 1906 many efforts, contributions and advances to characterise the fetal heart rate appeared in scene. By 1938, Bell recorded P waves using abdominal leads and major achievements occurred in the 1960s which is considered the decade of fetal medicine (Queenan et al., 2007). During this period of time Hon presented the use of electrodes directly attached to the fetus during labour with a marked improvement in signal-to-noise ratio (Hon, 1965), foreshadowing the use of electronic/computational/digital signal processing devices for FHR analysis.

1.2 Identifying the problem.

Nowadays the monitoring of the heart rate during labour still is not free neither of pitfalls or fatal outcomes, although there has been a great improvement in the way the fetus is monitored and diagnosed, the need for improving the fetal journey of being born, avoiding ominous episodes of hypoxia, asphyxia and other factors that can jeopardise the fetal life, persist.

A possibility to cover this need is through the use of the digital signal processing of physiological signals particularly the fetal heart rate, where the application of algorithms, mathematical concepts, physiological analysis and electrical measurements merge, allowing the application of electrical and electronic concepts to provide important contributions in favour of the fetal well-being.

Since the interpretation of the fetal heart rate depends on how data are collected and signals are monitored the rest of the chapter describes how the fetus is currently being assessed and data collected during labour and delivery.

1.3 Fetal monitoring.

Fetal ante and transpartum monitoring provides valuable information about the health of fetus, allows characterization of its development and detection of abnormalities. Can be performed by several methods, the choice of which method to use depends on how the pregnancy and delivery work evolve and if some type of risk have been previously diagnosed to the future mother (Gibb and Arulkumaran, 1997).

1.3.1 Auscultation

Consists in listening to the fetal heart beat in the same trend suggested centuries ago by using a stethoscope, and also through the use of Doppler ultrasound, where a transducer is pressed against the mother's abdomen, and the ultrasound device transforms the high frequency sound waves into signals related to fetal heart beats.

This technique of auscultation has been practiced with high success. However it requires to be performed by a well trained nurse or clinician, that would "never" have to leave the bedside of the patient (Freeman et al., 2003).

1.3.2 Electronic Fetal Monitoring

Electronic fetal monitoring consists in the use of electronic equipment to detect the fetal heart rate, this type of monitoring is performed using the following techniques:

Fetal electrocardiograms

To obtain the fetal heart rate directly from the fetal ECG it is necessary to wait until the rupture of membranes at the second stage of labour, to introduce a bipolar spiral electrode when the cervix is dilated about 2 cm. The electrode will be directly attached to the fetus head. Although this method presents good signal to noise ratio, sometimes, due the nature of the labour, it is not possible to be used or it is not recommendable, also detachment of the

scalp electrode can occur introducing spurious information, and the risk of injury and infection due the scalp fixation is present.(Murray, 2007, Cunningham et al., 2009). Attempts have been made to improve the scalp electrode device, proposed by Hon, aiming at not requiring penetration of the skin (Hofmeyer et al., 1993, Spencer and Samson, 1998, Antonucci et al., 1997). From the FECG recorded, different waves and intervals can be obtained to analyse the patterns of fetal heart rate, changes in the ST segment have been related to hypoxia (Amer-Wålin, 2008). However the main drawbacks encountered with this method were and are until now: Its use is limited only during the second stage of labour after membrane rupture; the risk of infection is present and small cut in the baby's head due the scalp electrode may occur, this wound can become infected and evolve to cranial osteomyelitis (Brook, 2005, Eggink et al., 2004), an too much time already had passed without a clear feedback of the fetus status, considering an average first stage of labour last more or less 13 hrs from the start of the contractions until fetal descent (Cunningham et al., 2009). However this approach represents one the most accurate methods to monitor, record and extract the fetal beat-to-beat heart intervals.

Fetal scalp blood sampling

In this method an endoscope is introduced also after membrane rupture and cervix is dilated, this device is pressed firmly to the fetal scalp and an incision is made on the fetal skin to get a drop of blood from which the pH is measured. Since the placenta is the only source of oxygen of the fetus, a reduction of the blood flow, consequence of the cord compression of the placenta, will alter the transfer of carbon dioxide from the fetus to the mother, and a decrease of the pH and high pCO₂ can be registered, and if the acidosis is transitory the FHR patterns improves, if not, damage to the tissue could be start occurring. Although pH measurements can identify fetuses with high distress, neither normal or abnormal blood samples have been shown to be a predictive of fetal outcome (Cunningham et al., 2009).

Serious complications of internal monitoring due to injury by the fetal scalp or by breach of the electrode such as the eye, are rare but can occur in case of fetal face presentation or during catheter insertion the penetration of the placenta, could end in haemorrhage and infection that has led to serious morbidity and spurious recordings (Trudinger and Pryse-Davies, 1978). Moreover certain maternal infections, including herpes, hepatitis B and hepatitis C, had been reported as contraindications to internal fetal monitoring, therefore this method is less used in comparison with the fetal scalp electrocardiogram (American Academy of Pediatrics and Gynecologists, 2007).

External Monitoring

Due to the proper nature of the labour when the scalp fetal ECG is not available or direct measurement of the ECG is not recommendable, the fetal heart rate can be obtained by a series of different methods, the use of Doppler ultrasound has been one of the most frequently used technique to monitor the FHR (Freeman et al., 2003). Its main advantage is that it is not invasive. It can be assumed that a measurement of the FHR will be possible during pregnancy and regardless of the stage of labour. Its operation is based in projecting an ultrasound beam, usually in the range of 1-2.3 MHz towards one of the main arteries of the fetus, the reflected beam from blood (and from the artery walls and/or valves) is slightly shifted in frequency as consequence of the blood flow. The Doppler signal is demodulated and the extraction of the fetal heart rate is performed, however the Doppler ultrasound signal has a complicated waveform product of reflecting the movement of the fetal heart and opening and closure of the valves as well as the blood flow, moreover the intermittent reposition of the Doppler transducer translates in a signal varying in time, making of his analysis a real challenge. Several studies had suggest that the Doppler ultrasound signal is a reliable source to obtain the FHR, with similar accuracy to the scalp fetal ECG. (Peters et al., 2004, Roj et al., 2008, Voicu et al., 2010)

Fetal heart rate patterns

The study and analysis of the fetal heart rate patterns have been used to observe the status of the fetus, the pattern analysis is a combination of observing the fetal heart rate and the uterine contractions along the time called cardiotocography (CTG).

1.4 CTG Physiology

Cardiotocography merges the words ‘cardio’ referring the heart rate and the word ‘toco’ derived from the Greek word for birth, and refers to uterine activity. Each word represents a particular signal: the FHR for the first one and the uterine contractions for the latest. Acquisition of the FHR can be done by the use of the scalp fetal ECG or by non-invasive Doppler ultrasound, the uterine contraction signals can be obtained from an intra-uterine transducer or by a non-invasive transducer located in the womb of the mother. Figure 1.1 presents the components of the CTG

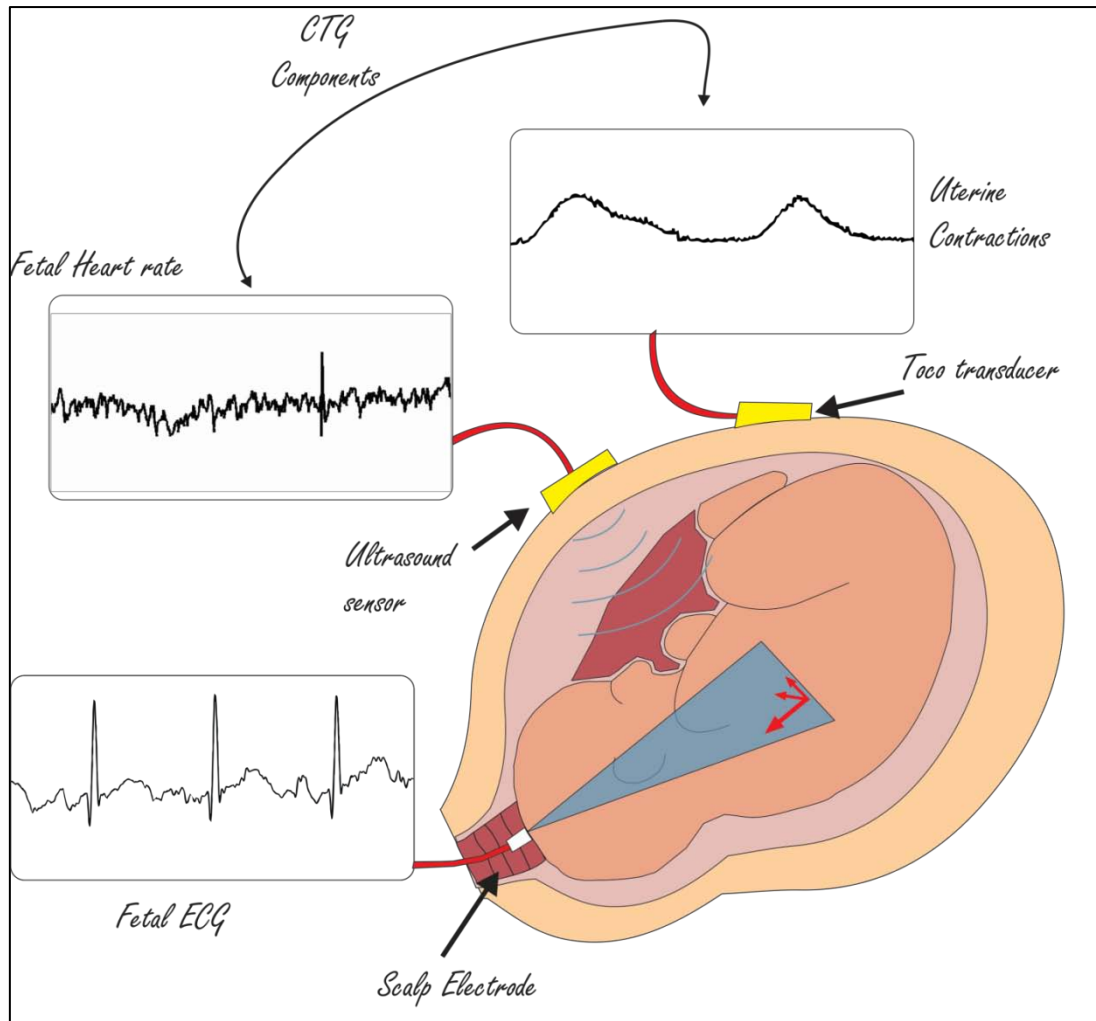


Figure 1. 1 Acquisition of the traces for the CTG

The contractions have a direct impact in the blood supply of the fetus at the end of the first stage of labour with the uterine activity presenting an amplitude of 50 mmHg and a duration of 60 s, with a frequency of 3 to 5 contractions every 10 min, with a relaxation time of 51 s in the first stage of labour and 36 seconds at second stage (Nama and Arulkumaran, 2009). The ideal contraction interval, that would ensure enough amount of oxygen to the fetus is 2-3 min (Gibb and Arulkumaran, 1997). The CTG pattern analysis follows the changes in the FHR in relation with the uterine contraction trace, and with basis in the morphology produced along time, the clinician can perform a diagnosis.

Although the use of this FHR monitoring technique has been a point of discussion for a long time the CTG has been reported to have a high sensitivity for the presence of spontaneous decelerations 99% (Chung et al., 2001) which reflect several physiological factors that we will describe along this chapter.

1.5 Placenta Blood Flow and changes in the FHR

The amount of oxygen that the fetus receives depends on the blood supply that arrives from the placenta through the umbilical cord, that is continuously challenged during labour and delivery, by several factors. The most dominant factors are the uterine pressures generated early in a contraction producing cord compression, mainly in the thin-walled umbilical vein (Cunningham et al., 2009). This will result in a reduction of the cardiac output with an initial compensatory increase in the fetal heart due the blood is pushed from the placenta towards the fetus, the heart needs to pump more blood. If the cord compression intensifies the umbilical arteries are also compressed, inducing an increase in the blood pressure. This activates the baroreceptors that will stimulate the parasympathetic system and the FHR will decrease, i.e. decelerate. As the contraction towards to the end the cord compression is relieved, first in the umbilical arteries. With this the elevated systolic blood pressure will drop and the deceleration of the FHR will be over, a final increase in FHR is seen as a result of persistent umbilical vein compression/occlusion (Cunningham et al., 2009). Once the uterine contraction and cord compression are over, the fetal heart returns to baseline.

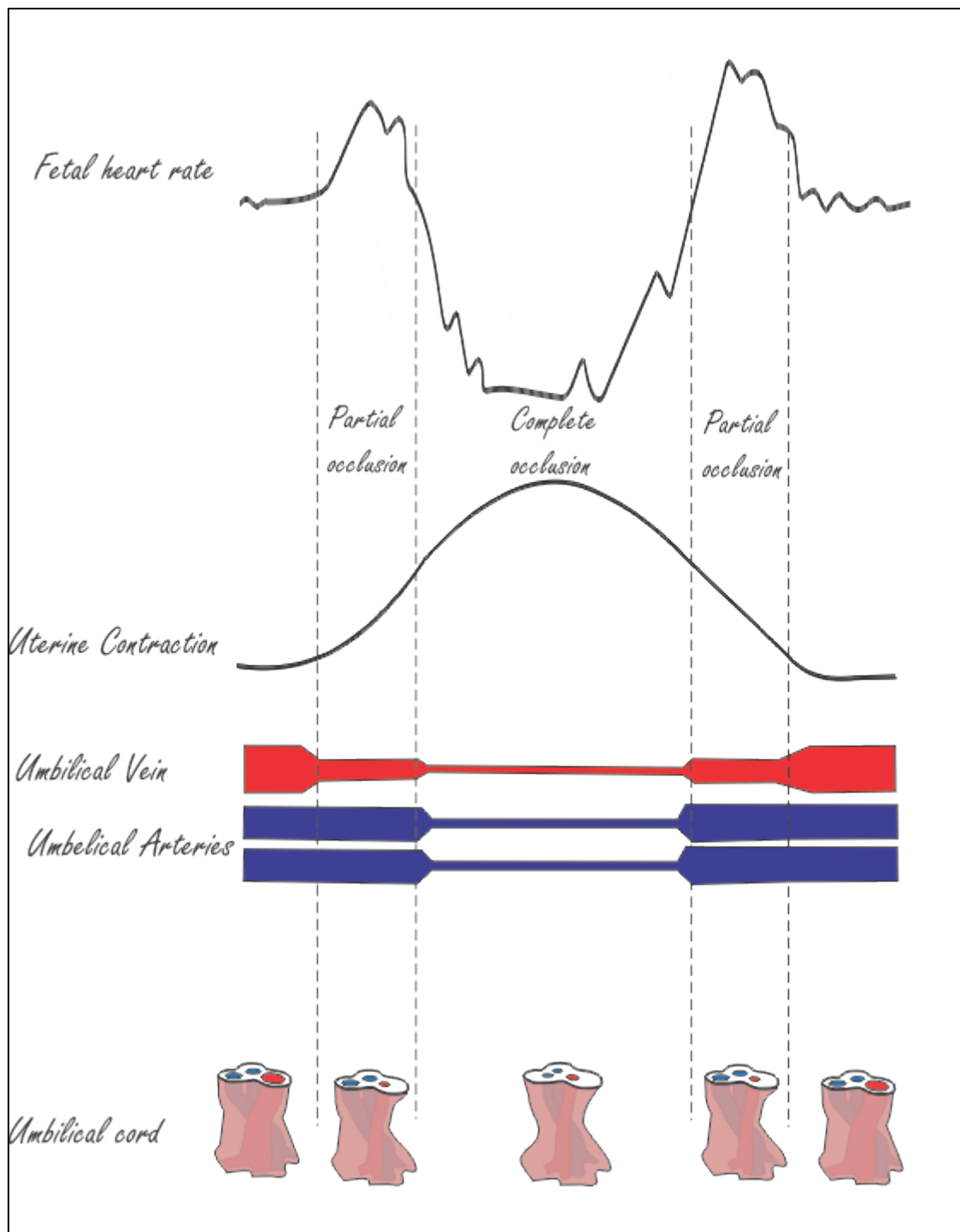


Figure 1. 2 Changes in the fetal heart rate due the compression/occlusion of the umbilical cord.

1.6 CTG classification and FHR monitoring concepts

In 1997 the National Institute of Child Health and Human Development proposed a standard to evaluate the FHR patterns which are the keystone of the CTG analysis (NICHD, 1997). Where the traces that can be observed in a CTG have been classified in accelerations and decelerations departing from a baseline of FHR. The definition of how to setup this baseline has been approached in different ways. From a wide literature review it is evident that the baseline is an essential part of the analysis of the CTG as without fitting this factor the quantitative analysis of the FHR, measurement and characterization of accelerations and decelerations is not possible. The FHR pattern components can be periodic and non-periodic. These are descriptive terms that are used to illustrate the time accelerations and decelerations that occur in response to contractions. If the accelerations and decelerations occur in relation to a contraction they are considered periodic changes otherwise they will be non-periodic. (Murray, 2007).

1.6.1 Baseline

Has been defined as the mean value of 10 min of FHR excluding acceleration or decelerations. The baseline decreases as the nervous system of the fetus matures. The normal base line is defined between 100-160 bpm for term and post term fetus, and 120-160 bpm for preterm fetuses. (Sundström et al., 2000).

1.6.2 Baseline variability

The FHR normally presents beat-to-beat variations which are not accelerations or decelerations as illustrated in figure 1.3, normal variability during labour is in a range of 5 to 25 bpm (Sundström et al., 2000, Arulkumaran and D'souza, 2009). It has been defined that the variability can be classified as short term variability and long term variability (Murray, 2007). This bandwidth of the variations of the heart rate can be used as a measurement of the

heart rate variability, but an important point that needs clarification is the concept of variation and variability. Variation must not be confused with variability. Considering that by definition variation is a measure of the difference between things and variability is the quality of being different. Variation usually is measured in milliseconds and variability in bpm. Both of them can be determined using Doppler ultrasound or scalp FECG. It has been said that using the latter reduced the precision of the variability measures due the averaging process embedded in the method used to detect the heart beats.

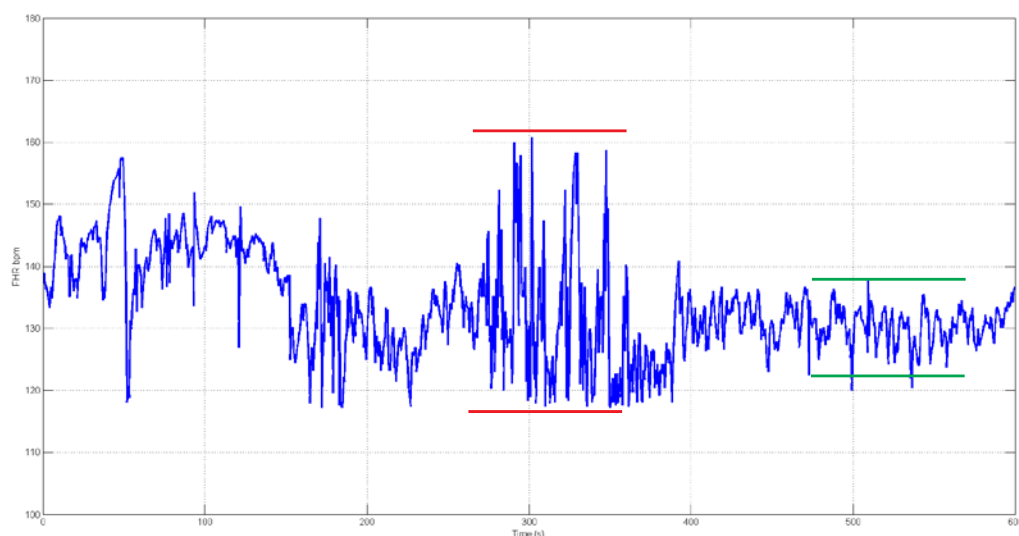


Figure 1. 3 The red lines indicate a high or saltatory pattern (an increase of more than 25 bpm in variability and the green lines indicate normal variability in the bandwidth of 5-25 bpm.

1.6.3 Accelerations

Accelerations is defined as an increase in the fetal heart rate of more than 15 beats per minute lasting 15 seconds or more. They are visually easy to identify and they usually manifest themselves in an abrupt increment from the base line (Arulkumaran and D'souza, 2009). A reassuring CTG typically contains at least 2 accelerations during a period of 20 minutes (Sundström et al., 2000), their presence are considered a good indicator of perinatal outcome, reflecting a good fetal oxygenation (Freeman et al., 2003, Gibb and Arulkumaran, 1997),

although their absence in the FHR tracing is not necessarily an ominous sign (Cunningham et al., 2009)

1.6.4 Spontaneous accelerations

These can last from 2 seconds to 2 minutes or more, their duration and non-periodic characteristics are the main differences from typical accelerations. They reflect stimulus of the sympathetic nerve (Aladjem et al., 1977) and are very common, being usually present in 99.8% of the CTG tracings of healthy fetuses (Krebs et al., 1982), suggesting a coordination within the central nervous system (Baser et al., 1992).

1.6.5 Uniform accelerations

Characterized by an increase of the FHR in response to stimulation of baroreceptors and chemoreceptors activated when the umbilical cord is partially compressed (Murray, 2007), they present a progressive onset and offset.

1.6.6 Decelerations

Decelerations are a drop in the fetal heart rate, usually for more than 15 beats, with a duration of at least 15 s (Murray, 2007, Sundström et al., 2000), they are sub-classified in relation of their shape as follows:

1.6.7 Early decelerations

Are gradually progressive, looking like a decrease in the FHR starting shortly after the onset of the contraction, could be as late as 20 sec. preceding the contraction, and can reach the lowest value of the contraction in 30 sec. or more, facing the peak of the contraction (Murray, 2007). They generally don't drop from more than 40 beats from the baseline (Arulkumaran

and D'souza, 2009), typically are caused by head compression, therefore usually are handled well by the fetus because they are not related with hypoxia (Sundström et al., 2000).

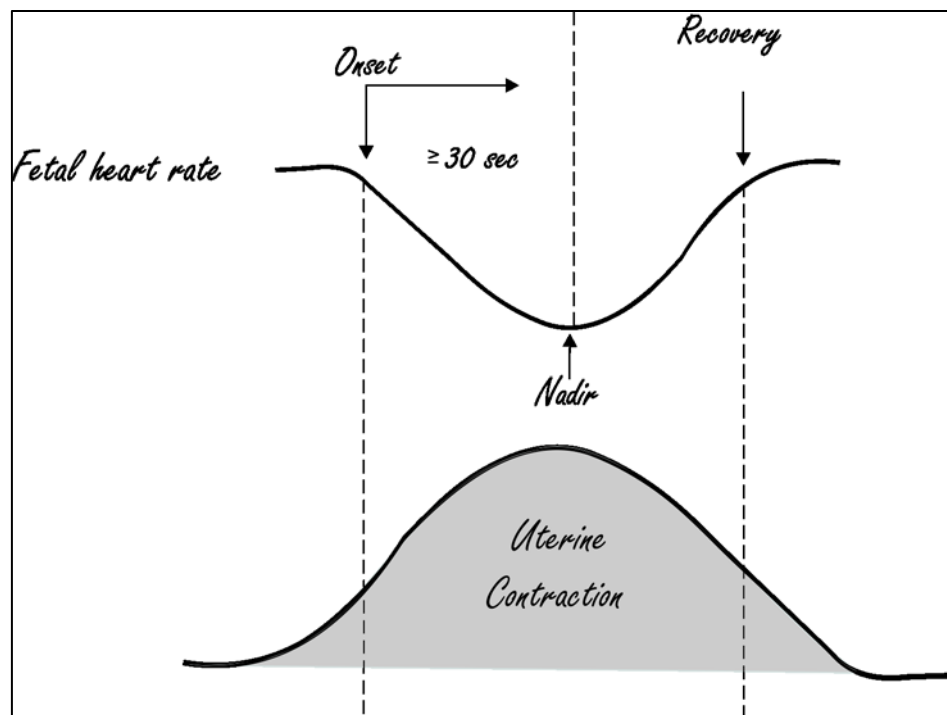


Figure 1. 4 Early decelerations patterns are characterized by the coincident peak of the contraction with the nadir of the deceleration

1.6.8 Late decelerations.

They are a smooth and progressive drop of the heart rate, with onset at the middle of the contraction typically with a lag of 30 sec. or more and ending after the contraction. They are related with intermittent hypoxia caused by reduction of the placenta blood flow. They are periodic and their depth can reach 60 bpm (Murray, 2007).

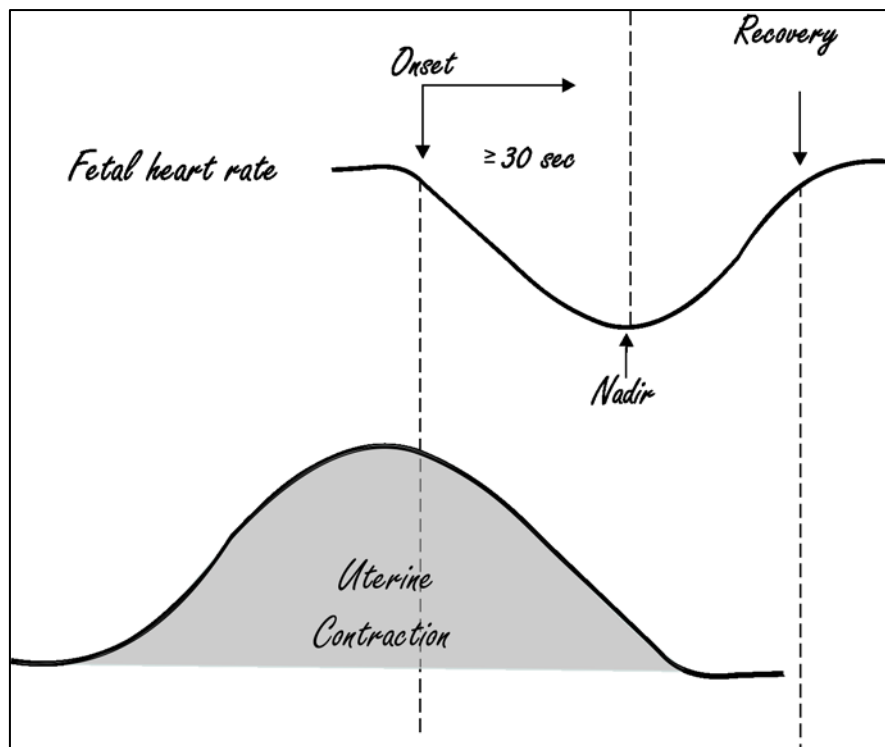


Figure 1. 5 Late decelerations are characterized by the nadir being out of phase with the peak of the contraction.

1.6.9 Variable decelerations

This type of deceleration is the most common among them, corresponding to 80% of all decelerations (Sundström et al., 2000, Cunningham et al., 2009). Visually they present an abrupt decrease in the heart rate. If the deceleration exceeds 60 sec. it is classified as complicated, where there is a risk of hypoxia development. The depth of this type of deceleration can be less than 70 bpm (Murray, 2007), they present a slow return to the baseline, (late recovery). The speed of the recovery on the ascending trace may reflect the blood flow and the resilience of the fetus (Gibb and Arulkumaran, 1997). We propose a method to address this particular issue in the next part of the chapter.

1.6.10 Prolonged decelerations

They are non-periodic isolated decelerations of FHR that last more than 2 min and less than 10 min, with a drop of 15 bpm (Freeman et al., 2003). They are difficult to classify in terms of pathophysiology, because they may have been seen in a multitude of situations, such as umbilical cord compression, uterine rupture among others (Murray, 2007).

1.6.11 Deceleration recovery time

From the FHR patterns previously described, the decelerations are directly associated with cord compression and hypoxic episodes. It is clear that slight or even severe episodes of hypoxia can be handled by a normal fetus (LaManna et al., 2011), even deep and brief decelerations are well resolved by the fetus adaptive mechanisms. However this transient hypoxia could evolve to chronic hypoxia scenarios. Other possibility is the “fatigue” of the fetus mechanisms to respond to high frequency of hypoxic events. From an animal model even healthy sheep fetuses when suffer continuous cord compression episodes for no so severe and brief periods, but in a repetitive trend, they developed severe acidosis and hypotension (Yagel et al., 2009). In the human fetal scenario this follow the same trend, an increase in the possibilities to develop chronic or severe acidosis. Therefore it is important to monitor the trend of recovery time/speed from the nadir of deceleration towards the baseline of FHR. Complementing this approach analyzing the FHR trace looking for frequently deceleration episodes, if there is a frequently slow recovery, it could be a marker to detect the starting point of a sever hypoxic event.

However to link a specific heart pattern to a clinical situation has not been clearly possible in all the cases, a fetus can present prolonged heart rate decelerations in 10 minutes and no problem or diseases has been encountered (Bohem, 1975). Moreover Melchior and

Bernard observed that only 1.4 percent of more than 7000 deliveries did not have decelerations during the second stage of labour (Melchior and Bernard, 1985).

Since FHR monitoring using this method is a process of recognition, the usual patterns can be identified, but when subtle patterns or those that occur from time to time appear, they are frequently not appreciated or missed completely (Freeman et al., 2003) thus the interpretation of the fetal heart rate patterns does not give an ideal prognosis of the fetal outcome.

1.7 Fetal distress

‘Fetal distress’ was often used to describe clinical scenarios where the maternal-fetal relation is compromised in such degree that fetal mortality and morbidity may occur, associated with the presence of fetal acidosis and fluctuations in the heart rate patterns (Haverkamp, 1979, Haesslein and Niswander, 1980), it could reflect the severity of fetal hypoxia (Myers, 1973), Nonetheless an ominous outcome wasn't always the result of distress episodes (Parer and Livingston, 1990).

Thus there is no precise definition of fetal distress: The term is too broad and vague to be applied with any precision to clinical situations (Cunningham et al., 2009). Instead the terms ‘non-reassuring’ and ‘reassuring’ have been suggested, to evaluate the patterns of FHR and classifying them in one way or the other (Yagel et al., 2009).

But these patterns during labour are dynamic, going from non-reassuring to reassuring and vice versa, making difficult to the clinicians to diagnose without doubt a particular condition based in the pattern analysis of the fetal heart rate, so sometimes this classification is considered controversial and imprecise (Cunningham et al., 2009).

Due to all this an ongoing question is how to approach the difficulties that lie behind identifying 'fetal distress' from the fetal heart rate?

An approach to this is that since the heart rate is the reflect of the interplay of several physiological signals and systems, and physiological systems are characterized by rhythms, that are not always periodic, their variability can be studied to yield insight information of the complex properties that define its very nature. In the past twenty years there has been a generalised interest in the study of the variability of the heart rhythm (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), looking forward to identify heart rate patterns and variations that could be specific to a particular pathology/clinical situation. With this an interesting and challenging quest arisen, the study and understanding of the variability of the fetal heart rhythm during labour and delivery, where a good comprehension of how the heart rate of a newborn changes due stress, gestation and other factors has been a long pursuit.

1.8 Ongoing scenario

It is clear from a comprehensive literature review that during labour and delivery the information extracted from the heart rate could help to interpret ambiguous heart rate patterns and with this avoid or recommend surgical interventions. The use of electronic fetal monitoring keeps growing in popularity for continuous surveillance of fetal heart rate, to study the fetal life, fetal development, fetal maturity and existence of congenital heart disease and diagnosis of advancing hypoxia which, if uncorrected, will produce fetal damage and in the worst case scenario fetal death (Thacker et al., 1995, Rosén and Kjellmer, 1975).

Nevertheless 30 years have passed since the introduction of the electronic fetal monitoring and still there is not a clear/accurate way of identifying the neonates with asphyxia (that can occur for several reasons, i.e. compression of the umbilical cord, abruption

of the placenta, abnormal uterine contractions or failure of the neonate to successfully begin breathing) (de Haan et al., 2006). The idea of having a time window that could avoid complications and fatal outcomes will depend in an exponential behaviour of the fetal distress, which is not the case, because from pathological scenarios it is very clear that the amount of time for diverse complications to become fatal is not the same for all the foetuses (Solt and Divon, 2005), therefore the need of a sharp method to identify delicate FHR behaviours during pregnancy and if required at any stage of labour.

Continuous recording of the fetal oxygenation would be the ideal method to assess fetal well-being, though until now no such technique is available, instead fetal brain oxygenation can be measured indirectly by monitoring the fetal heart rate, this presents an opportunity window for the analysis and study of the many physiological factors and elements that influence the behaviour of the pacemakers of the fetal heart (Solt and Divon, 2005), the rhythm at what these elements interplay varies by nature, and the study and analysis of these phenomena could present valuable information to contribute to fetal well-being.

1.9 Overview of this thesis

Through the use of HRV defined as the variations in the beat-to-beat intervals of heart rate, a non-invasive approach to provide information about the sympathetic and parasympathetic branches of the autonomic nervous system (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) important insights into the fetal cardio respiratory control system can be obtained. Several linear and non-linear methods and techniques have been proposed to analyse these beat-to-beat variations, reflecting different elements that drive the heart rate, and since hypoxic periods are characterized by an increased activity of the sympathetic and parasympathetic nervous systems, it would be possible to identify changes related to this clinical scenario.

The organization of the remaining of this thesis is as follows:

Chapter 2 focuses in the study of the physiology and control of the fetal heart rate, describing the elements that participate in the genesis of each beat, the factors that influence the activity of the fetal cardiovascular system, and discusses how to measure the electrical activity of the heart.

Chapter 3 is devoted to the analysis of the methods used for quantification of the heart rate variability, linear and non-linear techniques have been suggested as possible options, each of them showing different advantages and disadvantages that we will comment and discuss upon.

Chapter 4 presents and discusses the results obtained from analysing the HRV from an animal model/experiment where Wistar rats were submitted to different controlled periods of asphyxia (0, 1, 3, 5, 7 min). RR intervals time series were extracted from an electrocardiogram signal and both linear techniques: time domain and frequency domain and non-linear techniques: detrended fluctuation analysis, complexity analysis and Poincaré (plots and indices) were used for the study. A comparison of the measurements made before, during and after the asphyxia was induced was performed aiming to identify pronounced changes in a marker/index that would reflect in a accurate way the presence and amount of injury due to asphyxia.

The first part of chapter 5 centres in describing the work performed for the extraction of the beat-to-beat intervals of heart rate from signals obtained using a fetal monitor model HP8040A. Four signals were obtained: scalp fetal ECG, Doppler audio envelope, raw Doppler ultrasound and uterine contractions (TOCO). They were collected at 2000 samples per second (Schlindwein et al., 2004). Beat-to-beat intervals of heart rate were extracted from the scalp fetal ECG, and to extract the beat-to-beat intervals of heart rate from Doppler

ultrasound we proposed the use of three methods: Autocorrelation function, Wavelet transform and Hilbert-Huang transform, we compared the beat to beat intervals obtained from each method against the RR intervals obtained from the scalp fetal ECG as benchmark/gold standard. The second part of chapter 5 describes the use of HRV analysis to the beat-to-beat intervals of heart rate obtained from the fetal scalp ECG and from the Doppler ultrasound, following the same trend that we used to detect and study the asphyxia episodes in the animal model, the differences between the detections and HRV values are commented.

Chapter 6 describe the data analysis performed between FHR Decelerations and uterine contractions, to measure the time that it takes the fetal heart rate to return to baseline after reaching the lowest part of a deceleration, and the influence of the frequent spontaneous deceleration in the recovery time after decelerations.

Chapter 7 presents a summary of the techniques used and their performance to measure the beat-to-beat variability of intervals de heart rate, and recommendations of which should be the ones to be used in a future research.

Chapter 2

Fetal Heart Rate

“We cannot discover new oceans until we have the courage to lose sight of the shore” Muriel Chen.

2.1 Introduction.

The genesis of each beat of the fetal heart is the result of a complex interplay of different systems and elements within the fetal organism and its surroundings. Several factors: autonomic and non-autonomic have an impact in the rhythm of the fetal heart. We present the main elements that participate in each stage of the heart cycle, and comment on how these elements respond to external and internal stimuli, modifying the contraction and relaxation periods of the heart. Also we give a description of how the electrical activity of the heart can be measured, a key part for the analysis of the fluctuations of the fetal heart rate.

2.2 Feta Heart Anatomy and Development.

The development of the fetal heart, fig 2.1., occurs shortly after the implantation of the embryo approximately at the 3rd week of gestation. The heart then takes between 7 to 8 weeks to develop from a simple tube in which the blood is pumped through a number of connected elements, until septation (formation of the septum), which leads to the formation of the four-chambered muscle organ (Yagel et al., 2009).

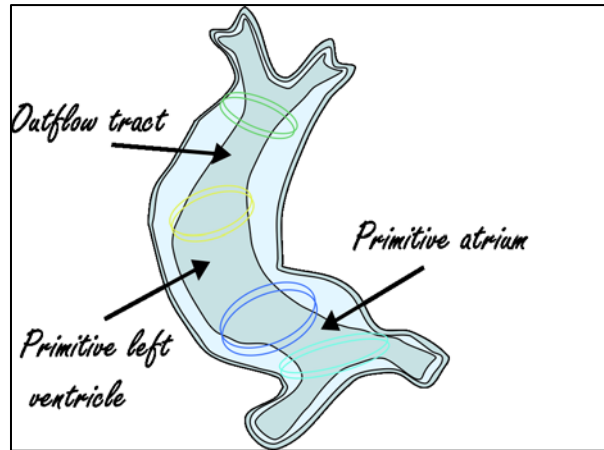


Figure 2. 1 Fetal heart during early stage of gestation, distinct atrial and ventricular cells can be described by the morphology of the tube, the coloured rings will shape the four chambered muscle during septation.

After week 20 the heart is mature enough to beat at 120-160 beats per minute and it can be heard even without amplification (Freeman et al., 2003).

Once the fetal heart reaches its full development, fig 2.2, there is a big resemblance with the anatomy of the adult heart, presenting a very similar electric activity but differing at the circulatory system (through in this chapter we will describe both of them).

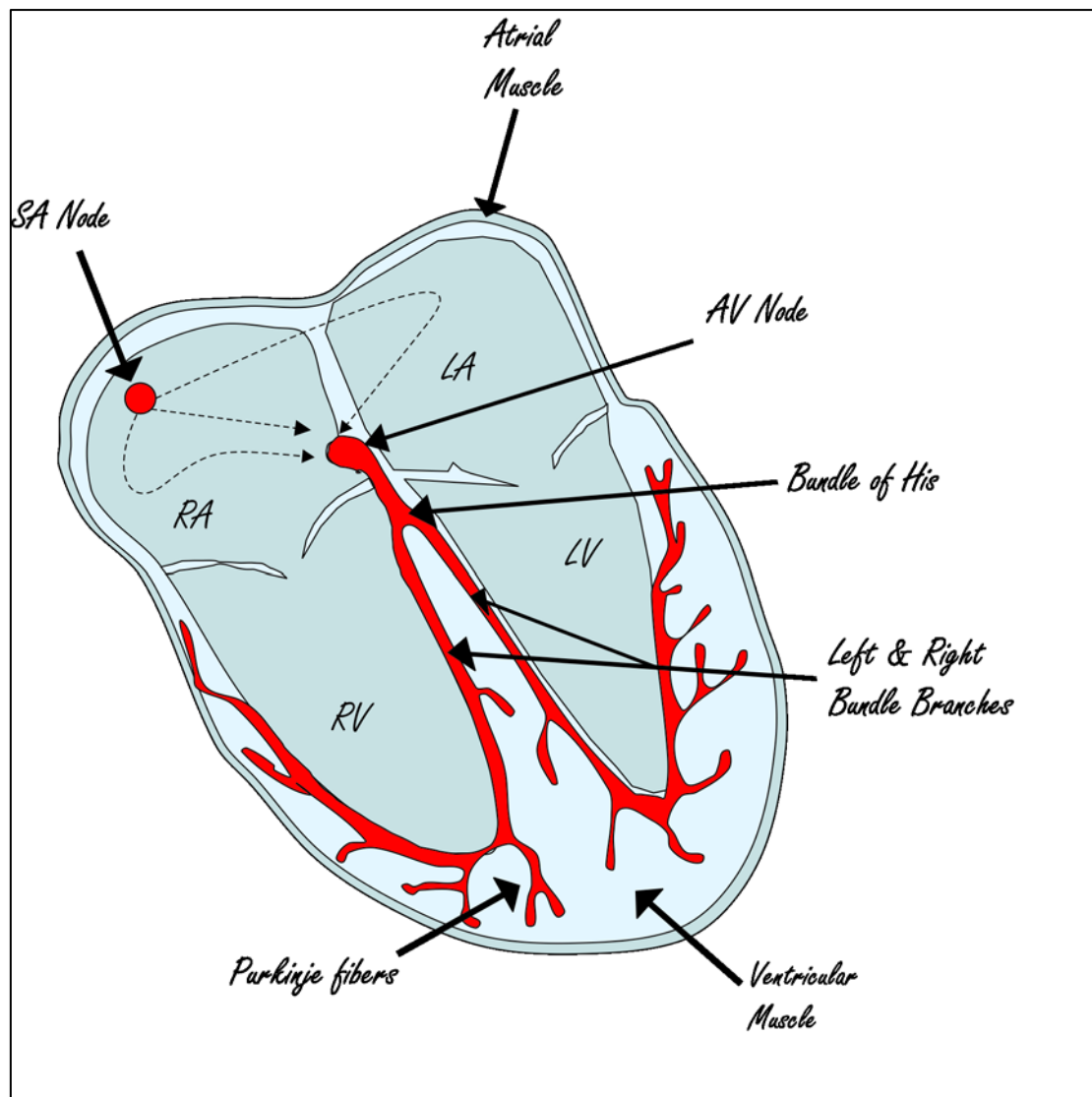


Figure 2. 2 The anatomy of the heart, fetus and the adult heart muscle elements are very similar. RA, LA, correspond to right and left atria and RV and LV to the right and left ventricle.

Once fully developed the heart at the core is a muscular organ in charge of pumping blood that contains oxygen and nutrients that allow the function of several systems within the whole organism and non oxygenated blood to the lungs. In case that the heart weren't able to pump blood any more, the organism will start to shutdown and after a short period of time will collapse (Aziz and Arif, 2010).

After septation the fetal heart is composed by four chambers that act as a pair of pumps: two upper chambers called atria (which receive blood from the veins of the circulatory

system) and two lower chambers called ventricles (in charge of the main pumping force), these four pumps are in charge of distribute the blood to the rest of the body. The anatomy of the heart is shown in figure 2.2.

2.3 Fetal Heart Circulation.

Until post-partum the fetal circulatory system of the fetus is very different compared to the newborn's, since the blood received from the mother through the placenta it has already been oxygenated, most of the blood in the right ventricle of the fetus does not pass by the lungs (that are not-functional/still in development), also the chambers of the fetal heart don't activate one after the other like in the adult, instead they pump blood at the same time, providing to the brain, heart and the rest of the body's extremities blood flow (Cunningham et al., 2009).

Therefore there is a 100% dependence on the blood (carrying the oxygen and nutrients), being supplied by the placenta, which is an organ part maternal part fetal, responsible for the transfer/delivery of oxygen and nutrients from the mother to the fetus and dioxide and metabolic waste from the fetus to the mother, although it seems that a mix of blood could occur in this action, there is not blood communication from the fetal capillars of chorionic villi containing the fetal blood and the maternal blood that stays in the intervillous space, of the chorionic villi. (Cunningham et al., 2009) fig.2.3.

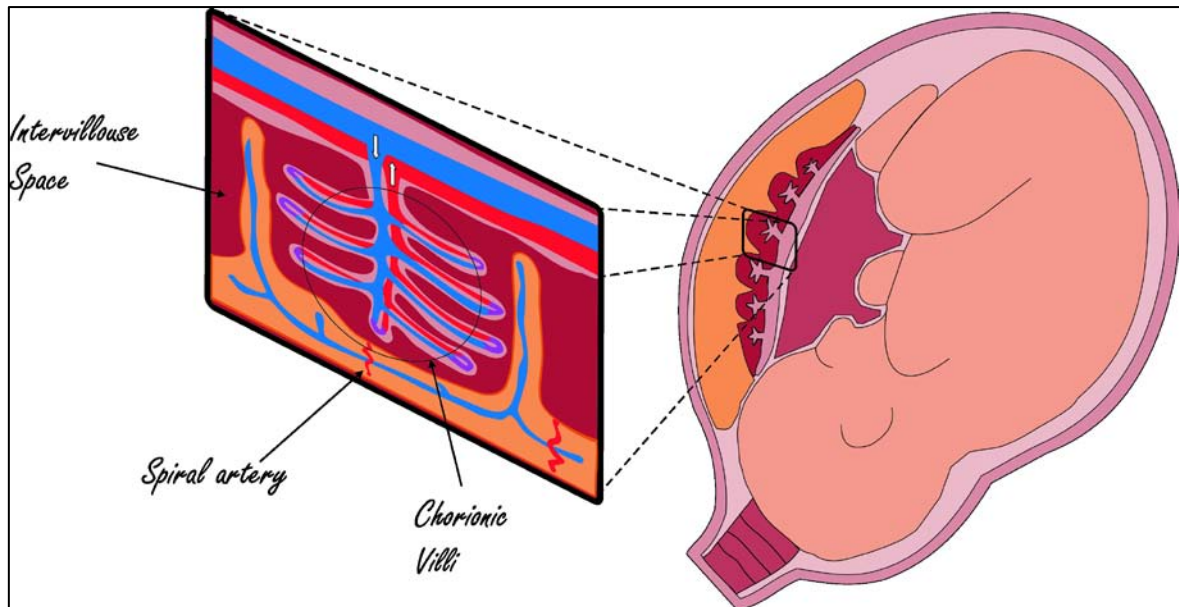


Figure 2. 3 Shows the Villus and the umbilical vein and arteries, main components of the mother-fetus transfer.

The jeopardy of the blood supply that flows through the umbilical cord fig 2.4 (arteries and vein) impacts the fetal oxygenation, where both factors influence a variety of interconnected mechanisms that drive the physiological control of the heart rate. (Cunningham et al., 2009)

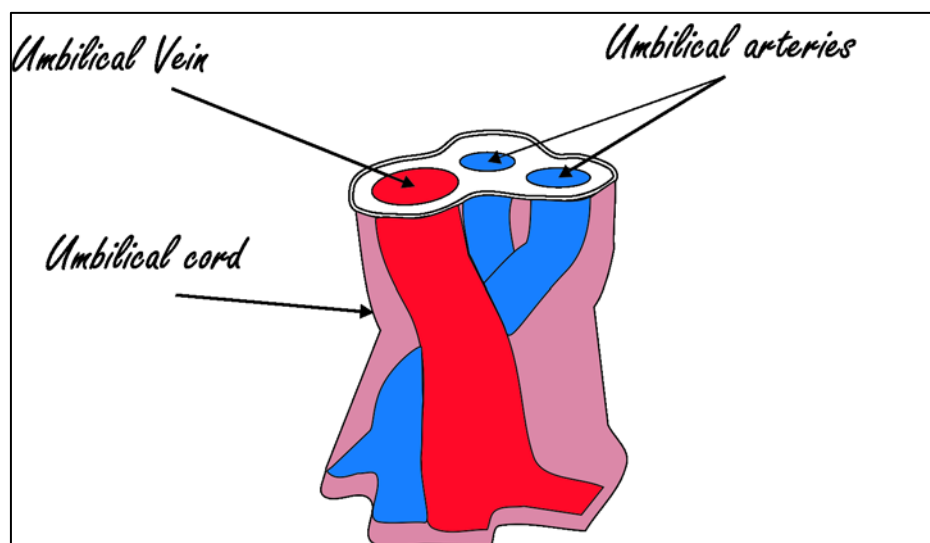


Figure 2. 4 Umbilical cord, the blood supply to the fetus is provided by a main vein

If the blood flow through the umbilical cord is poor/stops or if placenta insufficiency (low blood flow through the placenta) appears, the fetal supply of oxygen will start to run out, triggering an hypoxanemia status. If this situation is not reverted then the hypoxanemia will become hypoxia, even for acute hypoxia the fetus has a highly adaptable capacity thanks to reflexes that allow it to survive in a hypoxic environment (characteristic of inutero life), redistributing cardiac output in favour of the brain in response to the lack of oxygen, nevertheless if the hypoxia evolves/gets worse and becomes chronic hypoxia, which is clinically very common (maternal infection, placenta insufficiency, maternal inflammation, alcohol, abuse smoking undernutrition are all factors that can contribute to this), then fetal response will be a reduction on overall contractility (LaManna et al., 2011). If the insufficiency of oxygen persists, an asphyxia clinical scenario will be present, foreshadowing an ominous outcome for the fetal life (Freeman et al., 2003, Gibb and Arulkumaran, 1997, Amer-Wålin, 2008).

2.4 Fetal Heart Electric Activity.

The heart is driven by electrical impulses that depart from localized nodes within the cardiac muscles. These muscles are conformed by a peculiar group of tissues that possess a characteristic feature of being capable of depolarize and repolarise without the need of any external influence, unleashing electrical impulses that disseminate through the whole heart muscle and produce contractions and relaxation stages in a coordinated manner. This translates in a pumping action that, as we mentioned before, is essential for the oxygenation of the organism. The contraction activity must occur in a coordinated and timed manner to guarantee an efficient pump action on the blood, which in first instance must drawn the atria and then be derived into the ventricles before being pumped out by the action of the muscle walls that act like a squeezing fist (Keener and Sneyd, 1998).

The SA node initiate the depolarization impulse which in turn initiates an action potential that spreads through all the atria to the AV node here the impulse is delayed briefly before continuing on the ventricles through the AV bundle, bundle branches and Purkinje fibres, action potentials which spreads from the auto-rhythmic cells to the contractile cells are electrical events the subsequent contraction of the cardiac cells is a mechanical event that causes the heart beat.(Acharaya et al., 2007, Murray, 2007) Figure 2.5 summarizes the electrical components involved in the generation of the heart beat.

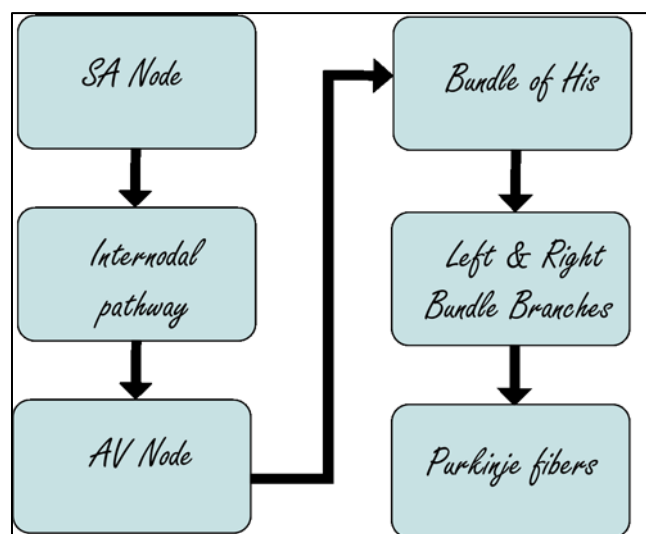


Figure 2. 5 Electrical conduction components of the human heart

Therefore the rhythm of the heart muscle is determined by this particular group of cells that produce electrical impulses, their discharge rate determines the heart rate, typically expressed as the number of times that the heart contracts per minute. After myocardial depolarization the tissue that just has been activated enters in a refractory state, preventing a constant myocardial depolarization (Yagel et al., 2009).

The main method used to analyse this electrical activity is the electrocardiogram (ECG) (Einthoven, 1895). The fetal ECG is a recording of the small voltage potentials across the skin of the mother or fetus scalp. The described electrical impulses can be detected by

invasive or non-invasive methods, the electrical impulses measured invasively have superior quality in comparison to non-invasive measurements, their advantages and disadvantages will be commented later in the chapter.

2.5 Electrocardiogram

With more than ten decades of history until now is the most common tool used to study the complex electrical conduction system of the heart, that drives the depolarization and polarization of the heart tissues (Cosío et al., 2009). Through its analysis it is possible to study the heart rhythm normal or abnormal, and the conduction through atria and ventricles .

There are different physiological factors that can be observed through the analysis and study of its component waves, isoelectric segments (time duration between waves), and intervals (time periods that include waves and segments) of variable length. These elements are described as follows:

2.5.1 P wave

Produced by depolarization of the atria prior to contraction. Due the small amount of muscle present in the atria, both the duration and the amplitude of this signal are small. In a healthy fetus at term typically presents a duration of 50-52 milliseconds (Pardi et al., 1974)

2.5.2 QRS Complex/Waves

Ventricular depolarization produces a cluster of waves that usually are referred as a single multiphase complex which typically starts with a small negative deflection (Q wave), next a large positive deflection occurs (R wave) and it finishes with a small negative deflection (S wave).

2.5.3 T Wave

The T wave corresponds to ventricular repolarisation.

Some times after the T wave some measurements have recorded the presence of another wave, U wave, product of the repolarisation of the Bundle-His and Purkinje fibres (Hurst, 1998).

The general amplitude of the fetal ECG trace is low, and in some cases it is very difficult to detect all the elements that compose a cardiac cycle, in general the R waves are the most used markers to define the beat-to-beat intervals. Figure 2.6 shows the waves and intervals of a fetal ECG.

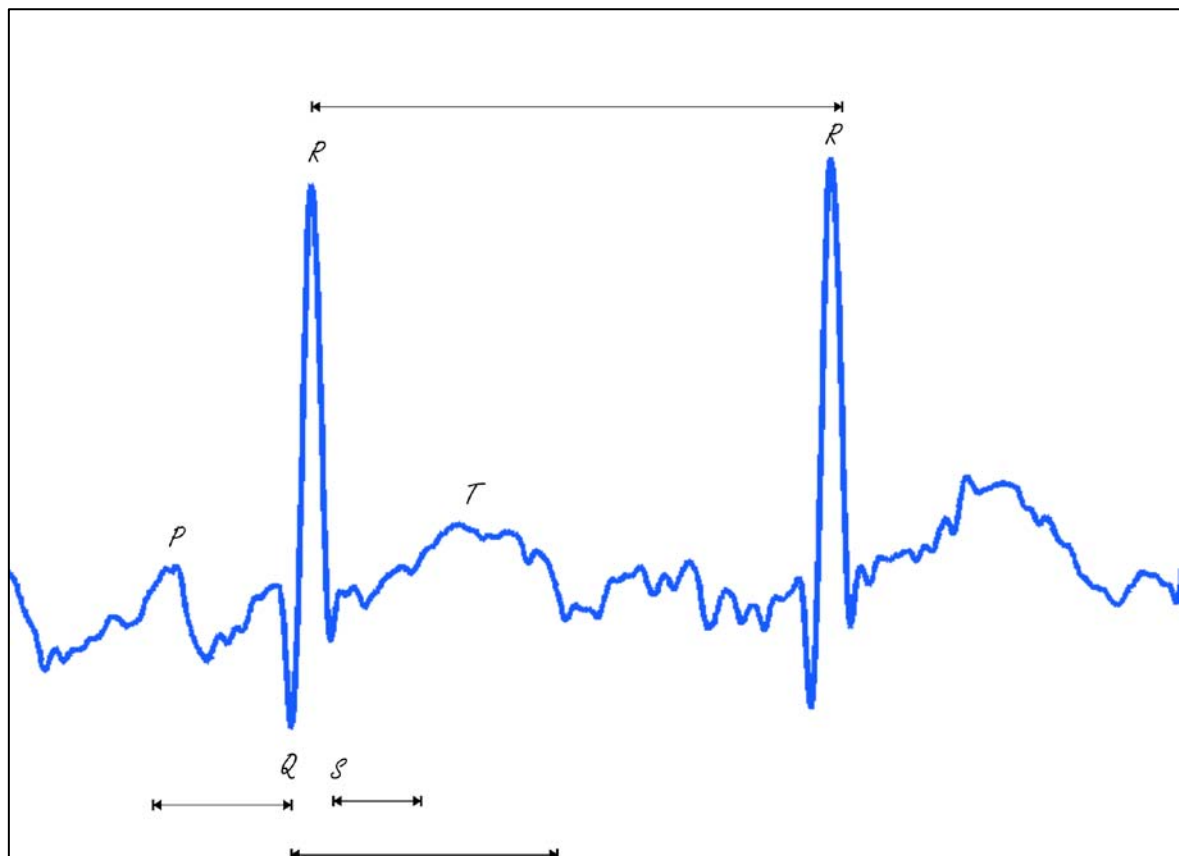


Figure 2. 6 Fetal electrocardiogram trace showing the main waves from which segments and intervals can be identified.

Although most of the studies that analyse the fetal ECG used the scalp electrode, there is also the possibility of using abdominal ECG, however as this method reported a low voltage and is usually very affected by several types of noise (Symonds et al., 2001), its use has been largely overcome by the use of Doppler Ultrasound technology.

2.6 RR intervals.

As we have described earlier, from the QRS complex the R wave is detected, since it presents a larger amplitude and high main frequency content over the rest of the waves, as well as much better signal-to-noise ratio. The time interval between two consecutive R peaks is known as the RR interval.

The series of RR intervals, known as RR interval time series or tachogram, is the most commonly used time series in the analysis of the heart rate variability. The RR interval time series used for HRV analysis should contain only normal RR intervals, as ectopic beats are generated differently and they don't carry information about the mechanisms that control the heart rate. Also unusual large P or T waves and myopotentials obscuring QRS complexes can produce spurious detections, these abnormal signals are known as artifacts and might be wrongly detected and affect the RR interval time series, therefore it is important to identify when an abnormal beat is detected and if the series should be corrected or not. This is commented in detail in chapter 3.

2.7 Fetal Heart Rate.

The instantaneous fetal heart rate represents the reciprocal of the interval between two consecutive beats and can be measured by the interval between two consecutive R waves (Freeman et al., 2003). This measure varies along the gestational period by the several mechanisms of maturation and by the influence of external stimulus. Usually a normal fetus presents an average baseline heart rate of around 140 bpm.

The vasomotor centre in the medulla oblongata regulates the control of the of the heart rate (figure 2.7), through the autonomic nervous system and via the carotid and aortic baroreceptors and chemoreceptors (Symonds et al., 2001).

2.8 Balance of the FHR by the Autonomic Nervous System (ANS)

The fetal heart has its own intrinsic activity and rate controlled by the sinoatrial node (SA) (Gibb and Arulkumaran, 1997), this is the natural pacemaker of the heart since its depolarization is the first to occur, inhibiting later electrical impulses produced by the other auto-excitabile cells. The AV node can also act as a pacemaker but with a lowest firing rate, translating in lowest heart rate. Both nodes are richly enervated by the sympathetic and parasympathetic branches of the autonomic nervous system.

The sympathetic system matures first, giving sense to a high baseline in preterm fetus (Gibb and Arulkumaran, 1997), the stimulation of this nerve drives the heart rate to increase. The parasympathetic system develops at the 8th week of gestation, but it is until week 32 when its activity seems to be reflected (Symonds et al., 2001), becoming more dominant over the sympathetic stimulation, which explains the decrease in baseline towards the end of the gestational period (King and Parer, 2000). Both systems interact constantly between them in a 'push-pull' trend, to produce a balance in the heart rate, but also interact and are influenced

by others physiological factors like baroreceptors, chemoreceptors and circulatory catecholamines.

2.9 Regulation of FHR by Chemoreceptors and Baroreceptors

Activity of the chemoreceptors (blood chemical sensors) and baroreceptors (blood pressure sensors), influence the heart rate. Chemoreceptors, located in the carotid sinus and other central sites are sensitive to changes in the oxygen and carbon dioxide content within the blood; an increment in carbon dioxide fires a signal from the chemoreceptors to the medulla oblongata, stimulating the parasympathetic system, in consequence slowing the FHR, this has been reported from experiments in fetal lambs where the stimulation of the peripheral aortic chemoreceptors results in parasympathetic stimulation and bradycardia, although still there is not yet a fully understanding of the role of the fetal chemoreceptors (King and Parer, 2000, NICHD and ACOG, 2009). The baroreceptors located in the aortic arch detect changes in blood pressure, when the blood pressure increases, a signal is fired through the vagal nerve to slowdown the heart rate, and a prolongation of the RR interval can be expected (Symonds et al., 2001).

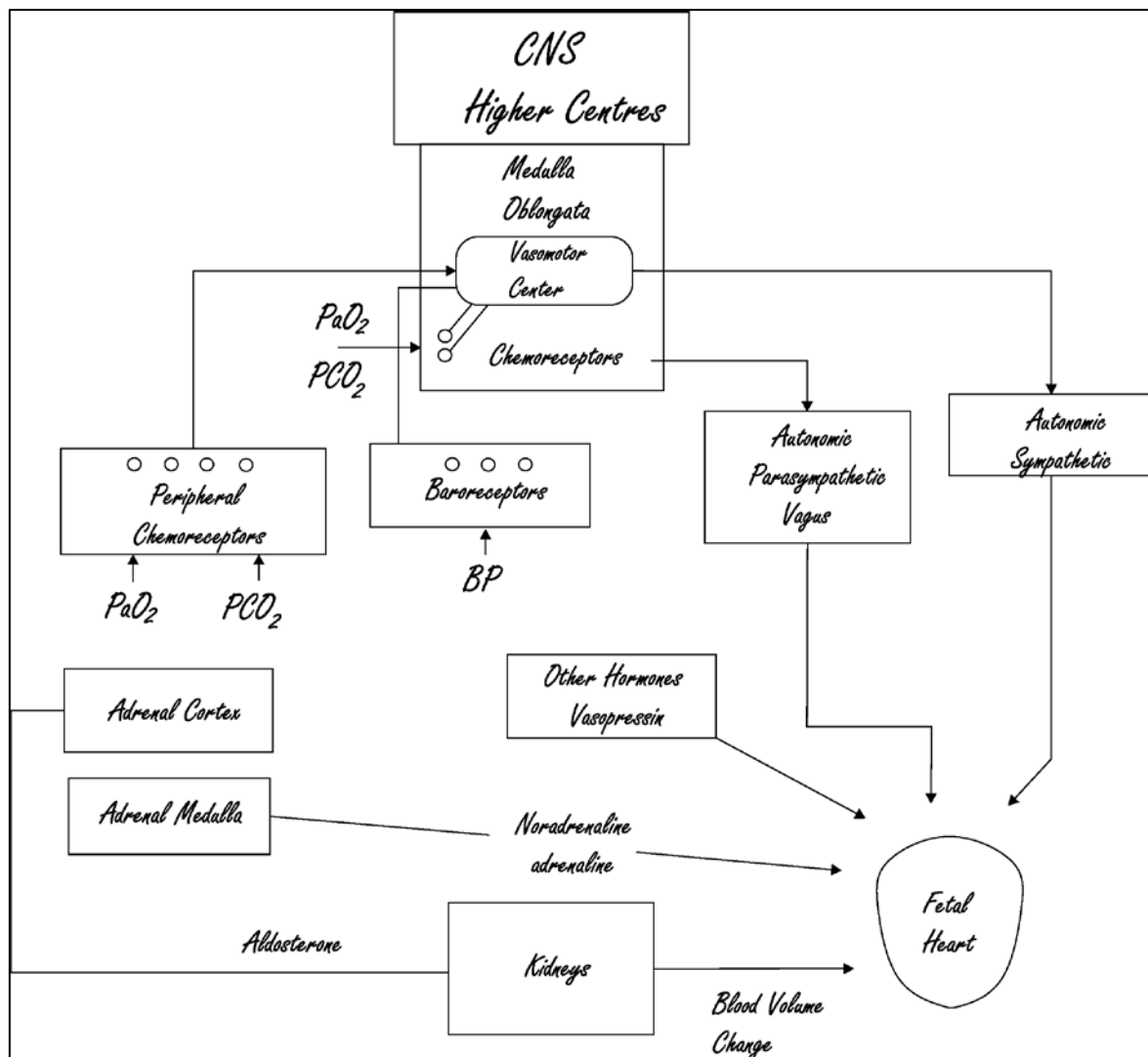


Figure 2. 7 Elements involved in the regulation of the fetal heart rate, CNS central nervous system, BP blood pressure, adapted from (Gibb and Arulkumaran, 1997).

Also the heart rate is influenced by the release of hormones (adrenaline, noradrenaline), from the adrenal medulla, insulin and thyroid. A release of catecholamines into the bloodstream in response to asphyxia/hypoxia can also increase the fetal heart rate (Pardi et al., 1977, Dalton et al., 1977).

2.10 Fetal Heart Rate Variability.

The heart rate variability can be defined as the variation on time of the interval between consecutive beats. For study and analysis it has been classified in:

2.10.1 Short term variability

Reflects the variation in time between consecutive beats, being influenced by the parasympathetic nerve (Symonds et al., 2001, Cunningham et al., 2009).

2.10.2 Long-term variability.

Portrays the variations that occur in no less than one minute (where the influence of the sympathetic and parasympathetic system have been suggested), (Symonds et al., 2001, Cunningham et al., 2009).

The interpretation and quantification of FHR and its variability relies on the understanding of the physiological factors that influence both of them, as we mentioned in chapter one, the pattern analysis of fetal heart rate can be considered very controversial, and more information can be extracted from the behaviour of the heart rate. Nowadays there are several mathematical approaches that have been applied to characterise its variability (see figure 2.8). Some of this techniques will be used in chapters 5 and 6, their full details and description are given in chapter 3.

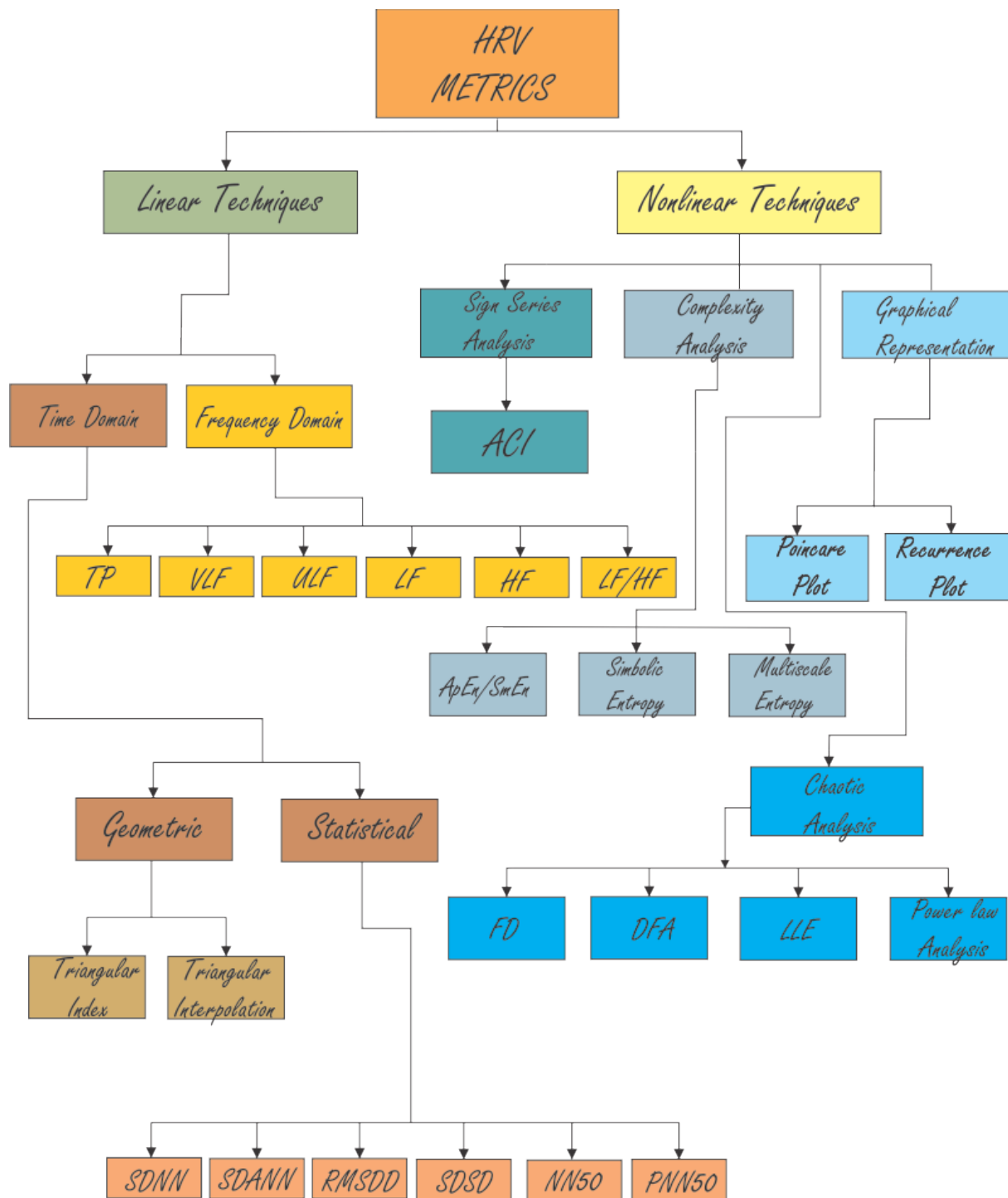


Figure 2. 8 Summary of methods used to quantify the HRV. Adapted from (Aziz and Arif, 2010)

2.11 Conclusions

Form the analysis of the physiology of the fetal heart it is clear that the sympathetic and parasympathetic systems play an important role in the control of the heart rate, thus it would be possible to assess the behaviour of each system through the variations of the fetal heart rate. It is however necessary to consider that other factors can influence the heart rate, as we have already described along this chapter. Moreover the own gestational process impacts on fetal heart rate, making the approach to be taken regarding what is happening more complicated.

The use of the electrocardiogram still is a fundamental part for the analysis of the heart rate, since the extraction of the beat-to-beat interval time series depends on the quality of the signal used to extract the intervals. The resolution and signal to noise ratio of the ECG trace compared with that of other signals is quite superior. Many advances have been made recently in Doppler Ultrasound technology and the heart rate extracted using an ultrasound-derived signal is now almost as accurate as the one using the FECG. We will address this topic in chapter 5. In the next chapter a deeper analysis of HRV is presented and a description of the metrics that can be used to quantify this phenomenon is given.

Chapter 3

Heart Rate Variability

“It is not important enough to have good mind, the important thing is to use it well” Rene Descartes.

3.1 Introduction.

Beat-to-beat interval variability was observed a long time ago. In 1733 Hales, noticed this phenomenon, decades had passed but without the computational advances and new processing techniques of nowadays, this physiological marker was not much considered regarding its clinical value. Much effort and contributions were made since and currently the analysis of the heart rate variability is considered a promising and powerful tool and in a not distant future it could be in common use by clinicians, in a similar way to the use of blood pressure, sugar levels, among other parameters. This chapter is devoted to the methods and techniques that can be used to quantify this phenomenon.

In the first part of this chapter we describe some of the benefits that until now have been possible to observe through its use, then we focus in describing the different methods to characterize it. First we comment about the use of linear methods and their applications, later we describe the non-linear techniques that have been used to analyse the HRV in short term and long term and discuss the peculiarities on the use of both kinds of methods.

3.2 Heart rate Variability.

After obtaining the RR interval time series (Described in chapter 2), the variability in the heart rate can be measured in any electrocardiogram recording of sufficient duration (Malik, 2004). As we mentioned before, the observation of the beat to beat fluctuation of the heart rate is not new, almost a quarter of century has pass since its discovery. But the lack of technology made the physicians to ignore it. Following computation and technological advances , in 1965 Hon and Lee observed that the fetal heart rate variability reflected fetal distress before any considerable change in the base line of the heart rate was possible to be appreciated (Hon, 1965). Since then a race has been unleashed where different methods and techniques had been proposed and used for assessment of HRV.

3.3 RR time series Pre-processing.

Heart rate variability metrics are obtained from the study and analysis of RR time series and special care must be taken before attempting any analysis of the beat-to-beat variability of this particular time series. Some steps that can be used are next listed: adapted from (Malik, 2004).

1. The signal-to-noise ratio must allow a good identification/location of the QRS complex.
2. The ECG signal must be regularly sampled and fiducial points must be located.
3. Rhythm and morphology of the QRS complexes must be classified to identify phenomena such as arrhythmia and others.
4. Ectopic beats and coupling intervals must be discarded and only RR intervals from normal sinus rhythm should be considered (these are named normal-to-normal NN intervals).

We should remark that the RR time series is a peculiar time series, where both axes represent time, one being related with the other. Additionally the time between the intervals is uneven by nature, because of the inherent variability in the heart rate that we are wanting to measure.

The methods and techniques used to quantify HRV can be grouped in two main categories: linear (time domain and frequency domain) and Non-linear (signal series analysis, complexity analysis and graphical representations).

3.4 Linear techniques.

3.4.1 Time Domain measures.

Time domain analysis include: 1) Statistical and 2) Geometrical methods for quantifying the HRV. These methods consider the RR time series as an unordered set of intervals measurements and applying different statistical means aim to measure the variance of such series (Malik, 2004). The statistical means of first order (mean) and second order (standard deviation) are calculated on beat-to-beat basis from direct measurements of NN intervals.

In 1996, the following group of statistical methods were suggested as ‘gold standard’, to perform HRV analysis (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). They provide results in units of time. Where RR_j denotes the value of the j 'th RR interval and N is the total number of successive RR intervals.

Statistical

- *SDNN(ms)* Standard deviation of all normal to normal intervals, can be calculated over different periods for short term variability (30s-5min) or long term variability (24h) (van Ravenswaaij-Arts et al., 1993, Aziz and Arif, 2010).

$$SDNN = \sqrt{\frac{1}{N-1} \sum_{j=1}^N (RR_j - \overline{RR})^2} \quad (3.1)$$

- *SANN(ms)* This method measures the standard deviation of the duration of the NN intervals averaged over 5 min periods for the full length of the recording (Aziz and Arif, 2010);
- *RMSSD(ms)* Square root of the average square differences between consecutive NN intervals;

$$RMSSD = \sqrt{\frac{1}{N-1} \sum_{j=1}^{N-1} (RR_{j+1} - RR_j)^2} \quad (3.2)$$

- *SDSD (ms)* Standard deviation of differences between consecutive NN intervals

$$SDSD = \sqrt{E\{\Delta RR_j^2\} - E\{\Delta RR_j\}^2} \quad (3.3)$$

- *NN50* Reflects the absolute count of consecutive NN intervals, differing by more than 50ms for the segment under analysis.

- *pNN50 (%)* Percentage of adjacent NN differing by more than 50 ms over a ECG recording of 24 hrs.

$$pNN50 = \frac{NN50}{N - 1} \times 100\% \quad (3.4)$$

Geometric Indices.

Since the statistical methods rely in the good quality of the NN interval time series (usually accomplished in short-term recordings) but longer records, usually there is a low precision of the QRS segments that, as we mentioned in chapter 2 represents the reference points to form the RR time series.

The statistical approaches are very sensitive to spurious values/outliers, modifying the outcome of the measure used by a considerable amount. The use of geometrical methods was proposed to overcome this kind of difficulties, as they are less affected by ectopic values.

HRV Triangular Index (HRV index)

Produced with the total number of all NN intervals divided by the maximum height of the histogram of all normal-to-normal intervals quantified on a discrete scale with bins of — where f_s = sample rate (Clifford et al., 2006).

TINN Triangular interpolation (ms)

Computed from the histogram of the NN intervals, obtained by approximating the NN interval distribution using an isosceles triangle and measuring its base.

3.4.2 Frequency Domain Measures

NN time series are constituted by physiological events, driven by different factors and elements (Chapter 2) that act in different frequencies. To get a better insight of how these elements influence the HRV the use of the frequency domain techniques has been suggested (Akselrod et al., 1981, Sayers, 1973). Prior to the use of these methods it is necessary to pre-process the NN time series that by nature presents intervals that are not equally spaced, thus this must be taken into consideration, if not, the spectral analysis of the HRV would have poor physical meaning (Kudryński, 2010).

Once that the RR time series is equally spaced, standard frequency domain analysis techniques provide very useful information of how energy content distributes as a function of frequency (Malik, 2004, Aziz and Arif, 2010).

Transformation from time domain to frequency domain is possible through the use of the discrete Fourier transform (nonparametric method), this transform is very common to implement and presents high computational processing speed, the NN time series is treated as a summation of sine waves of different periods where the contribution of each component of the summation is considered an estimate of the corresponding frequency spectrum. Alternatively one can use autoregressive model estimation (parametric method) as this technique provides estimates of the frequency spectrum with better spectral resolution for short time series. Either method allows easy post processing of the spectrum and calculation of HF and LF, location of each central frequency and accurate power spectral density, (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996, Malik, 2004).

The drawback of these frequency domain techniques is that compared with the time domain, they require more complicated mathematical operations being applied to the NN

time series and the compatibility and sensitivity of the chosen model need verification (Boardman et al., 2002a).

Since Sayers in 1973 performed frequency analysis in the heart rate and HRV spectral analysis was performed by Akselroad in 1981 (Sayers, 1973, Akselrod et al., 1981) a large number of authors have used spectral analysis, decomposing the NN time series into equivalent amplitudes and frequencies. To facilitate inter study-comparisons, the frequency spectrum of heart rate has been divided in four different spectral bands, to calculate the energy content in a reproducible trend (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), this has been suggested for adult, unfortunately in the case of fetal analysis there is no standard to follow, representing one of the problems to solve in the near future. Next we give a brief description of the characteristic of these bands.

ULF Ultra low frequency band VLF very low frequency bands

The range of these bands is $0.0001\text{Hz} \leq \text{ULF} \leq 0.003\text{Hz}$ and $0.003 \leq \text{VLF} \leq 0.04$. These frequency bands are used during long term HRV analysis, where variations of the heart rate due to fluctuations in blood pressure and temperature can be reflected (Kudryński, 2010). The ULF band is present when long term data is evaluated (Acharaya et al., 2007), and might reflect circadian and neuroendocrin rhythms. The VLF band reflects long period rhythms and is affected by temperature regulation and humoral system, an increase in the frequency content of this band indicates fetal distress (Ohta et al., 1999, Chung, 2001, Chung et al., 2001) nevertheless its physiological meaning is one of the most discussed (Acharaya et al., 2007).

MF Band

The range of this band is $0.07 \text{ Hz} \leq \text{MF} \leq 0.13 \text{ Hz}$ the fluctuations in this frequency range reflect fetal movements (Goncalves et al., 2006), and low values of this band are associated with the fetus presenting an arterial base deficit (Rantonen et al., 2001).

LF Low frequency band

The range of this band is $(0.04\text{Hz} \leq \text{LF} \leq 0.15\text{Hz})$

This band seems to reflect the baroreceptor reflex activity influenced by sympathetic and parasympathetic activity (Malik, 1995.) although it has been suggested that only the sympathetic activity is reflected (Eckberg, 1997), thus its origin has not yet been unquestionably explained, but a decrease in this band has been reported in cases of fetal distress in cases of fetal acidemia hypoxemia, also in growth retarded fetuses LF is suppressed in comparison with that normal fetuses or (Ohta et al., 1999, Salamalekis et al., 2006, Rantonen et al., 2001, Chung et al., 2001, Suzuki et al., 2001, Siira et al., 2005), and has been reported that the LF frequency has a sensitivity of 97.5% and specificity of 86,1% to detect fetal distress(Suzuki et al., 2001).

HF High frequency band

This final band has a range of $(0.15\text{Hz} \leq \text{HF} \leq 0.4 \text{ Hz})$ reflects the parasympathetic vagal activity (Akselrod et al., 1981, Akselrod, 1995) since is synchronized with the respiratory rhythms, it is sometimes called the respiratory peak (Aziz and Arif, 2010). Often the LF/HF ratio is used to assess the balance between the sympathetic and parasympathetic systems. Increased ratio seems to reflect healthy fetus as it responds to uterine contractions whereas severe acidotic fetuses don't present this response markedly (Oppenheimer et al., 1993, Romano et al., 2006).

VLF, LF, and HF are typically expressed in absolute values of power (milliseconds²), where the sum of the energy content of the three bands is known like total power (TP), but also LF and HF can be presented in normalized units to remark the tone balance of the mentioned systems (Malliani et al., 1991, Pagani et al., 1986), which represent the relative value of each frequency component in proportion to the total frequency content minus the VLF component (Malik, 2004), thus the normalization minimises the effect of changes in total frequency content on the values of LF and HF components.

3.5 NON-LINEAR TECHNIQUES.

A normal heart is not a perfect oscillator since it is under different physiological influences, therefore we can presume that non-linear phenomena is involved in the genesis of HRV (Babloyantz and Destexhe, 1988, Goldberger and West, 1987, Aziz and Arif, 2010), then standard linear techniques applied to the HRV analysis may not be able to reflect alterations and anomalies in the heart dynamics, where it seems that the systems involved in cardiac regulation interact between them in a non-linear way (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996, Pagani et al., 1986, Eckberg, 1997). This can be approached using mathematical methods, which go beyond the examination of the whole variability of the heart rate, aiming to quantify temporal complexity by analysing the components of RR time series in a selected length. (Acharaya et al., 2007).

In this section we present a review of the non-linear techniques most widely used for the study of HRV.

3.5.1 Power law HRV analysis.

Power law describes the dynamics that have similar patterns at different scales, reflects the distribution of power spectral density. To perform power law analysis it is necessary to obtain the power spectrum, after this the power analysis is obtained through plotting the log of spectral power against the log of frequency, from where is obtained a straight line with a negative slope. Power law analysis finds the nature of correlations along the frequency spectrum (Seely and Macklem, 2004). Power law analysis has provided in several clinical studies a parameter that is related with cardiovascular disorders (Bigger et al., 1996). The drawback of this method is that it needs to be performed in long term data to achieve statistical results.

3.5.2 Detrended fluctuation analysis.

This method was proposed in 1995 by Peng *et al.* and quantifies the presence or absence of fractal correlation properties of NN intervals, characterises fluctuations on scales of multiple lengths. It was developed specifically to distinguish between intrinsic fluctuations produced by complex systems and those caused by external stimulus (Peng et al., 1995). The principal advantage of detrended fluctuation analysis is that it can detect long-range correlation in non-stationeries NN time series. Unfortunately for a good outcome large amounts of data are required in comparison to other non-linear methods: At least 8000 data points have been recommended to be considered. More details about this method can be found in Peng *et al.* 1995.

This method can be thought as a modification of a root-mean square analysis applied to nonstationary signals (Acharaya et al., 2007). For its use the RR intervals are integrated in a time series by the formula

(3.5)

where $y(k)$ is the k^{th} value of the integrated/mapped series, $RR(i)$ is the i^{th} inter beat and the average inter beat interval for all the signal is given by $\bar{RR}$. This produces a series that is divided into equal boxes of length 'n', where n =total data points of time series/total number of boxes. In each box, the local trend is calculated as a linear representation of trend function in that box using least squares method. This series is then detrended by subtracting the local trend in each box and root mean square of this integrated and detrended time series called $F(n)$ is calculated by

$$F(n) = \sqrt{\frac{1}{n} \sum_{k=1}^n [y(k) - y_n(k)]^2} \quad (3.6)$$

By performing this calculation for all values of 'n' it is possible to graph the relationship between $F(n)$ and n . The slope of the graph between the $\log n$ and $\log F(n)$ is named scaling exponent (α). A linear relationship between $\log n$ and $\log F(n)$ appears to distinct linear segments, one for small n ($n < 11$) and one for large n ($n > 11$) (Aziz and Arif, 2010), producing two lines with two slopes α_1 and α_2 respectively that give us information about the particularities of the time series. The principal advantage of DFA is that it is able to detect long-range correlation in time series having nonstationarities, although it requires more data points (at least 8000) in comparison with other techniques.(Acharaya et al., 2007).

3.5.3 Poincaré plots/return maps

Poincaré plot is quantitative tool that can be used to analyse the NN time series for short-term and long-term studies (Brennan et al., 2001). In this method each interval of the NN time series is plotted against previous NN interval, the patterns obtained through this plot allow to distinguish healthy and pathologic subjects related with cardiac function by means of a visual interpretation, thanks to the ability of graphically showing nonlinear aspects of the NN time series. From these plots quantitative indices of short-term and long-term variability can be obtained (Brennan et al., 2001). The plot portrays the value of a given heart period (on the abscissa) against the subsequent heart period (on the ordinate) (Berntson et al., 1997), the dispersion points on the X and Y axes illustrate the overall range of the RR intervals (Doyle et al., 2009), the use of the shape of this plot is quite versatile has been used for categorize and classify even the degree of heart failure (Acharaya et al., 2007). The plot reflects the short term variability and long term variability and these can be quantified in the form of SD1 and SD2, which are the standard deviations that correspond to the distances of the R-R(i) to the lines $y=x$ and $y=-x+2R-R_m$, where $R-R_m$ is the mean of all R-R(i) (Rajendra Acharya et al., 2006).

Poincaré Plot Indices

Several methods have been proposed to quantitatively summarise the plots geometric distribution (Kamen and Tonkin, 1995), using standard time domain statistics and also fitting and ellipse to characterise the distribution of the points in the plot (Tulppo et al., 1996) or by fitting an identity line related to the Pearson's correlation coefficient (Otzenberger et al., 1998). The use of the Poincaré indices can be optimized as a quantitative tool by the use of different lags (Contreras et al., 2007), and researchers have shown interest in plots with different time delays to get better insight in the time-series signal

From SD1 and SD2 a further two measures can be computed to study the sympathetic and parasympathetic systems: Cardiac vagal index and Cardiac sympathetic index . This latter has been described as an indicator of the level of neural control influencing cardiac function and a sensitive indicator of the autonomic nervous functions in infants (Hae-Kyung, 2009).

Complexity analysis

Many studies on the physiology of the cardiovascular system have suggested that nonlinear chaotic dynamics are involved in the generation of the heart rate signal (Kikuchi et al., 2006).

Complexity analysis of the HRV has been proposed as an interesting alternative to approach this situation and as a complement to the traditional methods used for assessing the beat to beat interval variations at short and long term (Malik, 2004, Signorini et al., 2003). Approximated entropy analysis (ApEn) that allows to measure the irregularity (complexity) of a signal (in this case the heart rate). The outcome of this method has reported good results even when applied to short and noisy segments of data (Pincus, 1991), it presents a higher value in the case of normal RR variations and decreases as the variations of the RR decrease (Rajendra Acharya et al., 2006). Nevertheless the approximate entropy presents some pitfalls (mainly bias related with the length of the data) that can be covered by the use of the Sample Entropy, an improved version of the approximated entropy. This method, proposed by Richman and Randall (Richman and Moorman, 2000), addresses the problem of self matching, it is more consistent and less dependent of the length of the data

For both methods the parameter m defines the length of the vectors that are compared, and the parameter r acts as a filtering level or threshold, we will considered the values suggested for $r = 0.2$ (SDNN), and the value of 2 for m (Pincus and Goldberg, 1994). Where for both techniques the term N is the number of data points

3.5.4 Approximate entropy analysis

This method measures the regularity and complexity or randomness of the RR time series. It was first introduced by Pincus (Pincus, 1991) to measure the complexity of a system composed by relatively short and noisy data. To perform this analysis it is necessary to search for recurrent patterns in the NN time series (Aziz and Arif, 2010). This is achieved by selecting values with tolerance r , the regularity of patterns comparing them to a given pattern of length m , therefore m is the detail level at which the signal is analyzed and r is the threshold, which filters irregularities. (Ferrario et al., 2005)

Although the main advantage of the Approximate Entropy (ApEn) is that it may be calculated for short time series of data with good results (Pincus and Goldberg, 1994), even for small series of 50 data points, there is an inconvenient: The amount of data points can influence the obtained result (Malik, 2004), therefore there is a problem regarding the sensitivity to the size of the data. To overcome this problem, like we mentioned before the use of the Sample entropy is recommended (Richman and Moorman, 2000). To compute this parameter first a set of length m vectors u_j is considered:

$$u_j = (RR_j, RR_{j+1}, \dots, RR_{j+m-1}) \quad j = 1, 2, \dots, N - m + 1 \quad (3.6)$$

The distance between these vectors is defined as the maximum absolute difference between the corresponding elements.

$$d(u_j, u_k) = \max \{ |RR_{j+n} - RR_{k+n}| \mid n = 0, \dots, m-1 \} \quad (3.7)$$

Then for each u_j the relative amount of vectors u_k for which $d(u_j - u_k) \leq r$ is computed. This index is denoted like $C_j^m(r)$ and can be expressed like

$$C_j^m(r) = \frac{\text{number of } \{u_k | d(u_j, u_k) \leq r\}}{N - m + 1} \quad (3.8)$$

The normalization makes that the value of $C_j^m(r)$ always smaller or equal to 1, then the value of the natural algorithm of each $C_j^m(r)$ is taken and the average over j , and finally the approximate entropy is obtained as

$$ApEn(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r) \quad (3.9)$$

$$= -\frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln(C_r^m(i)) + \frac{1}{N-m} \sum_{i=1}^{N-m} \ln(C_r^{m+1}(i))$$

3.5.5 Sample entropy

This method follows in great manner the same approach of the ApEn approach but presents the advantage of being less dependent on the time series length and presents better consistency along ranges of possible values of m and r (Malik, 2004). Two main difference for its calculation are the number of vectors u_k for which $d(u_j, u_k) \leq r$ also the vector u_j it is included. This guarantee that $C_j^m(r)$ is always larger than 0 and the logarithm can be applied, but at the same time makes the ApEn to be biased, in the sample entropy the self-comparison is eliminated obtaining $C_j^m(r)$ as

$$C_j^m(r) = \frac{\text{number of } \{u_k | d(u_j, u_k) \leq r\}}{N - m} \quad (3.10)$$

Then the value of $C_j^m(r)$ will be between 0 and 1. Next the values of $C_j^m(r)$ are averaged to obtain

$$C^m(r) = \frac{1}{N - m + 1} \sum_{j=1}^{N-m+1} C_j^m(r) \quad (3.11)$$

And the sample entropy is obtained as

$$\text{SampEn}(m, r, N) = \ln(C^m(r) / C^{m+1}(r)) \quad (3.12)$$

This method has been used as an alternative to ApEn to measure fetal activity (Goncalves et al., 2006).

3.5.6 Acceleration change index

Another option to analyse the dynamics of the heart rate variability recently has been proposed by Garcia-Gonzales *et al.* 2003 (Garcia-Gonzalez et al., 2003, Aziz and Arif, 2010). This method detects the presence of very high frequency content on the NN time series, presenting a good behaviour in the presence of artifacts and noise (Aziz and Arif, 2010).

3.6 Conclusions

Along the last 10 years there has been a marked increase in the research of HRV, refining the measurements provided by the linear methods, the relative simplicity of some of them and the standardisation of the parameters for their use have made them very popular (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Through the use of the frequency domain analysis it has been possible to gain information related to the growth retardation and fetal movement (Brebrouiz *et al.* 1998), also observe reduced respiratory peaks in asphyxiated term neonates (Divon *et al.* 1986), and a better understanding of how the ANS activity is influenced by the fetal breathing movements (Karin *et al.*, 1992)

The absence of standardisation of frequency bandwidths makes the analysis less reproducible, therefore the resultant clinical point of view obtained using these methods could be, in some cases, contradictory (Van Laar *et al.*, 2008, Chung *et al.*, 2001), generating uncertainty about the information that can be extracted from this analysis, where in some cases there is no big difference in the frequency content of the spectrum before and after clinical scenarios (Sibony *et al.*, 1995). This could be because the maturation of the fetal ANS influences the hemodynamic response to stress, thus the frequency content in the LF and HF bands increases with the gestational age, thus it must be defined at what point of the period of the gestational period the ANS is mature enough to perform frequency analysis.

Also the dependence of stationarity is still a problem to solve. An alternative group of techniques that deal with the non-stationarity characteristics of the NN time series are the non-linear methods that have been used to yield new insights into the abnormalities of the heart rate patterns in various different clinical conditions. The use of the approximated entropy is becoming popular as a complement to the frequency domain analysis providing a

better comprehension of cardiac signals (Goncalves et al., 2006). Moreover, interesting results have been observed through the use of entropy indices comparing the fetal HRV before delivery and during delivery (Pincus, 1991, Signorini et al., 2003, Salamalekis et al., 2006) Using detrended fluctuation analysis it has been possible to observe a substantial change in the maturation of the fetal ANS from 26 weeks to 30 weeks of gestation (Padhye et al., 2006, Ferrairo et al., 2009) presenting an option to solve the issue of when it is appropriate to apply frequency domain methods.

From the medical point of view there is still some scepticism on the use of these mathematical models to improve medical scenarios. There is still plenty of work being done to prove the contrary. But in the mean time the combination of both types of methods, linear and non-linear, represents an excellent option to study heart rate variability. In the next chapters we will use some of these techniques aiming to find the best tool to identify variations in the heart rate that could detect distress due to asphyxia and quantify it.

Analysis of HRV before, during and after asphyxia periods

“Small opportunities are often the beginning of great enterprises” Demosthenes

4.1 Introduction.

In this chapter we describe an approach to detect asphyxia episodes and characterize them through the use of heart rate variability analysis, employing some of the linear and non-linear methods described in chapter 3. First we explain the extraction of the RR time series from collected electrocardiograms and then we focus in the analysis of the HRV, before and after asphyxia episodes.

Given the ethical constraints as well the difficulties to obtain data related to asphyxia during labour and delivery, the methods described in this chapter were applied to data arising from an animal model. Despite there being morphological and physiological differences between the adult animal model and the human fetal model, these data sets were the most appropriate option for field testing the HRV analysis methods covered in chapter 3.

This allowed us to start the analysis and characterization of signals to detect and classify asphyxia as its identification during labour can provide valuable information to help the clinical staff to intervene before damage to the fetus occurs (Freeman *et al.*, 2003).

4.2 Data Collection

The data analysed was collected from a series of experiments where 24 adult rats Wistar species were anaesthetised, intubated and had their femoral artery cannulated, each rat was submitted to controlled periods of asphyxia of different lengths: 0 (for two of the rats that were the control group), 3, 5, and 7 minutes.

The ECG signal was acquired at 333Hz using a 12-bit A/D converter, and recorded during 72 hours, after the experiment the rats were sacrificed for pathological purpose.

4.2.1 Beat to beat extraction

As we mentioned before the R peak is the easiest feature to identify from an ECG. Considering this we implemented QRS detection and the extraction of the RR time series from the collected electrocardiograms using a Butterworth band pass digital filter with cut-off frequencies of 5Hz and 36 Hz, to remove high frequency noise (such as the power line noise 60 Hz – the signal was collected at Johns Hopkins University, Baltimore, USA) and low frequency baseline wander. The threshold used for the detections of the R detections was adjusted heuristically and presented optimal detections when set to 65 % of the running average of the peak of the magnitude of the QRS complexes. A refractory period of 112 ms was employed to reduce the possibility of false detections of sharp T waves.

Since the electrocardiogram records can register a variety of spurious, ectopic and non sinus beats, these elements must be removed before analysing the time series otherwise the results will be influenced by their presence (Malik, 2004), therefore, we pre-process the signal containing the R-R interval time series to eliminate the contaminants previously described, and obtain the so called N-N interval time series. This process was as follows:

First we set of up a range to exclude RR intervals which were too long when compared to the preceding and successive beats

(4.1)

if they are we replace them with the interpolation of the successive beats by:

$$rr = \quad (4.2)$$

After this, we selected segments of the NN time series of 10 min length following the recommendations of the Task force, the segments that we selected were located before, and after the asphyxia for 5 min, 15 min, 25 min and 35 min. With this methodology we aimed to identify the occurring changes along the time for the different methods to characterise the heart rate variability. The time just after the asphyxia episode (i.e. the ventilator was unclamped) had to be discarded, because for the rats that were subjected to 3 min or more of asphyxia, an injection of adrenaline and mechanical ventilation restarting with 100% O₂ were performed to bring them back from cardiac arrest. We considered that after 5 min after the asphyxia, the effect of the adrenaline will be washed out of their system, and therefore the analysis will not reflect the resuscitation procedure.

4.2.3 HRV Analysis

We performed heart rate variability analysis by two approaches, using linear and non-linear techniques. For the linear approach we used methods of time domain: From the broad selection of statistical methods available for the analysis of the HRV, we implemented SDNN, the standard deviation of the normal to normal intervals, which reflects the cyclic variations caused by the neuro-control system (Kudryński, 2010); mean RR to obtain the average heart rate; RMSDD, the square root of the mean of the sum of the squares of differences between adjacent NN intervals (Clifford et al., 2006); mean HR and the Standard deviation of the heart rate.

We also applied frequency domain analysis to get a better approach and differentiate between the contributions of the parasympathetic and sympathetic systems that in some occasions are difficult to appreciate using time domain techniques only (Rajendra Acharya et al., 2006), and since frequency domain methods allow this by the decomposition of the FHR signal in its frequency components (Goncalves et al., 2006). In this work we used FFT-based spectrum analysis to compute sequential spectral estimates from 256-point long segments with an overlap of 50% and a Hanning window to reduce spectral leakage. For comparison, power spectral analysis was also determined by the use of parametric autoregressive (AR) modelling of order 20, since optimal results have been reported with the use of this order . Regarding the selection of the frequency bands for the spectral analysis there has been a standardization in the values to use when performing spectral analysis of signals from humans by the Task Force (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), however for the animal model there were no guidelines from the Task force, so, from an abridged literature review we selected the following values: low frequency LF(0.195 - 0.6 Hz), high frequency(0.6 - 2.5 Hz) to obtain the power spectral indices of HRV and ratio of LF to HF power (LF/HF).

And for the non-linear approach we applied Poincaré we obtained the Poincaré plots for each group before and after the asphyxia episodes, and from this plot we extracted the indices standard deviation 1, standard deviation 2, cardiac vagal index and cardiac sympathetic index. Finally the complexity analysis was completed using approximated entropy, sample entropy and detrended fluctuation analysis.

4.3 RESULTS

4.3.1 Time Domain Indices

The time domain indices obtained from the analysis of HRV allowed to clearly identify when the asphyxia was induced to each one of the groups of rats, indicating a possible marker for its detection, we evaluate which parameter allows a better appreciation of the transient insult. We obtained results to visualize the behaviour before asphyxia (10min of base line), during the insult (length depending of the group) and after the asphyxia (5min,15min,25min,35min), we grouped each cohort of rats 0 min (control), 1min, 3min, 5min and 7 min, and plot their results for each one of the HRV techniques, Mean RR (fig 4.1), SDDNN (fig 4.2), STDHR (fig 4.3), RMSDD (fig 4.4) , the results are expressed as mean $\pm$ standard deviation.

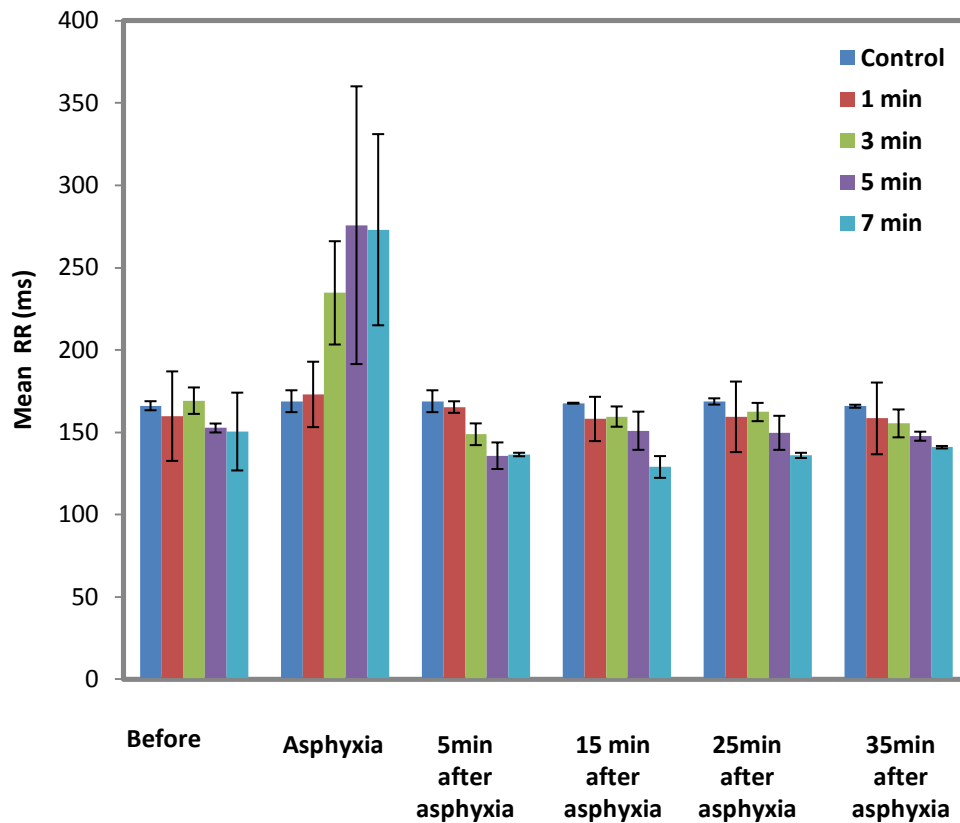


Figure 4. 1 Mean RR for the different groups of rats.

The increase in the mean RR during asphyxia is evident for the groups of 3,5,7 min, whereas the value for the group of 1 min did not reflected any considerable difference during the insult, that is, the mean RR seems not to be sensitive to mild asphyxia episodes. For the analysis before and after asphyxia, no change is noticeable as the mean RR value remained close to the base line value for all the groups.

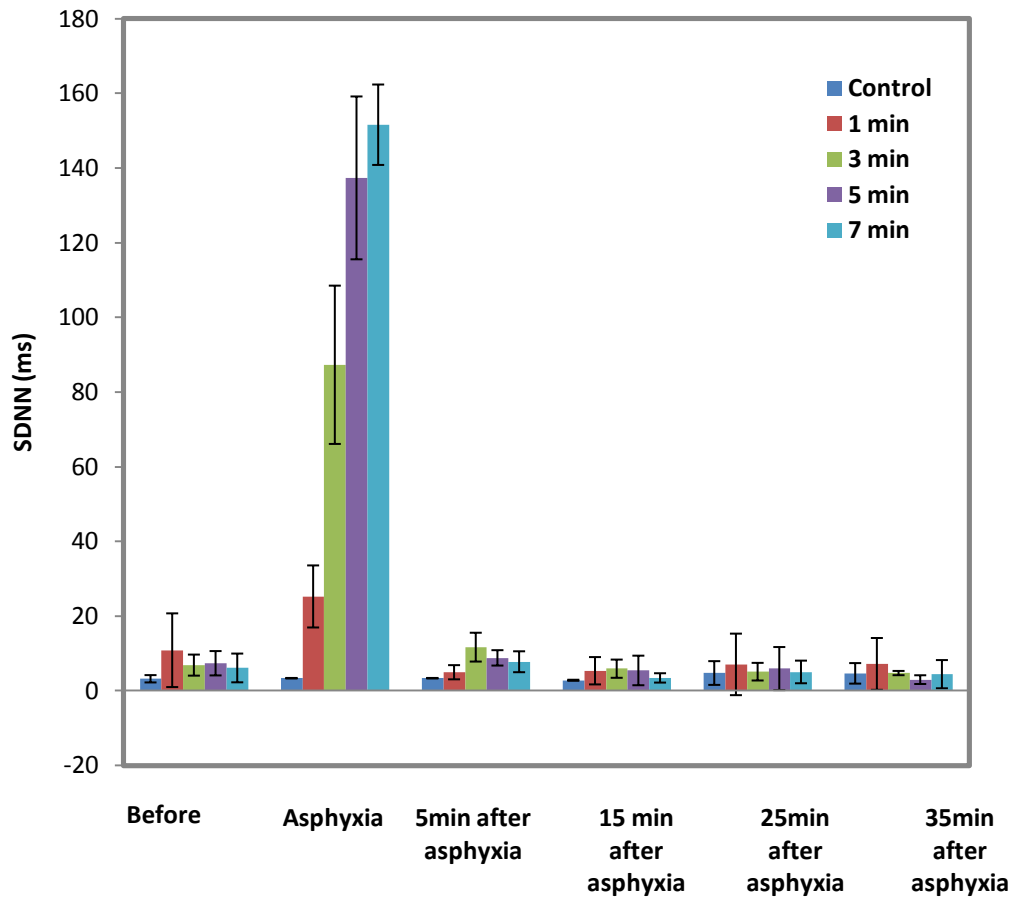


Figure 4. 2 SDNN for the different groups of rats

The SDNN during asphyxia presented a marked increase for the values of 3,5,7 min compared to their baseline values. The group of 1 min also presented an increase, not with the same magnitude of the other groups, but from the SDNN is easier to observe the transient asphyxia than from the mean RR as all the values increased in comparison with the base line.

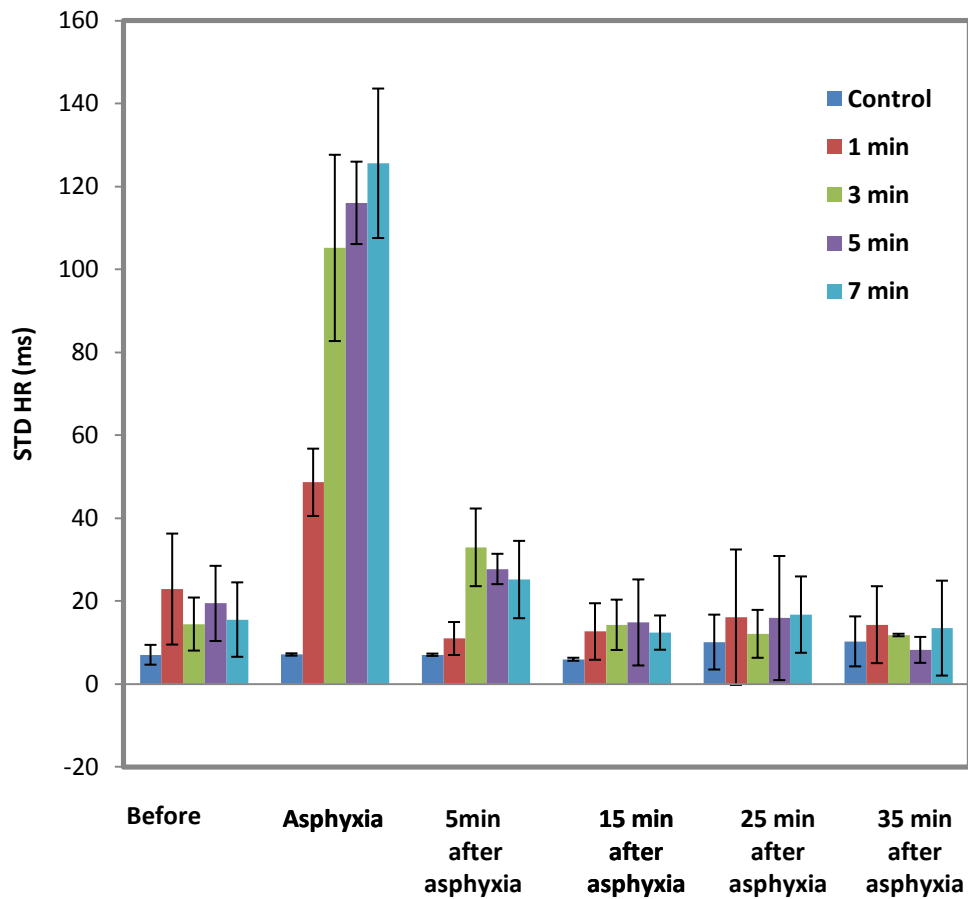


Figure 4. 3 STD HR for the different groups of rats.

The values obtained from the STD of HR presented the same tendency of the previous time domain methods, but the group of 1 min seems to be more sensitive to this technique, reflecting a more clear increase than in previous cases.

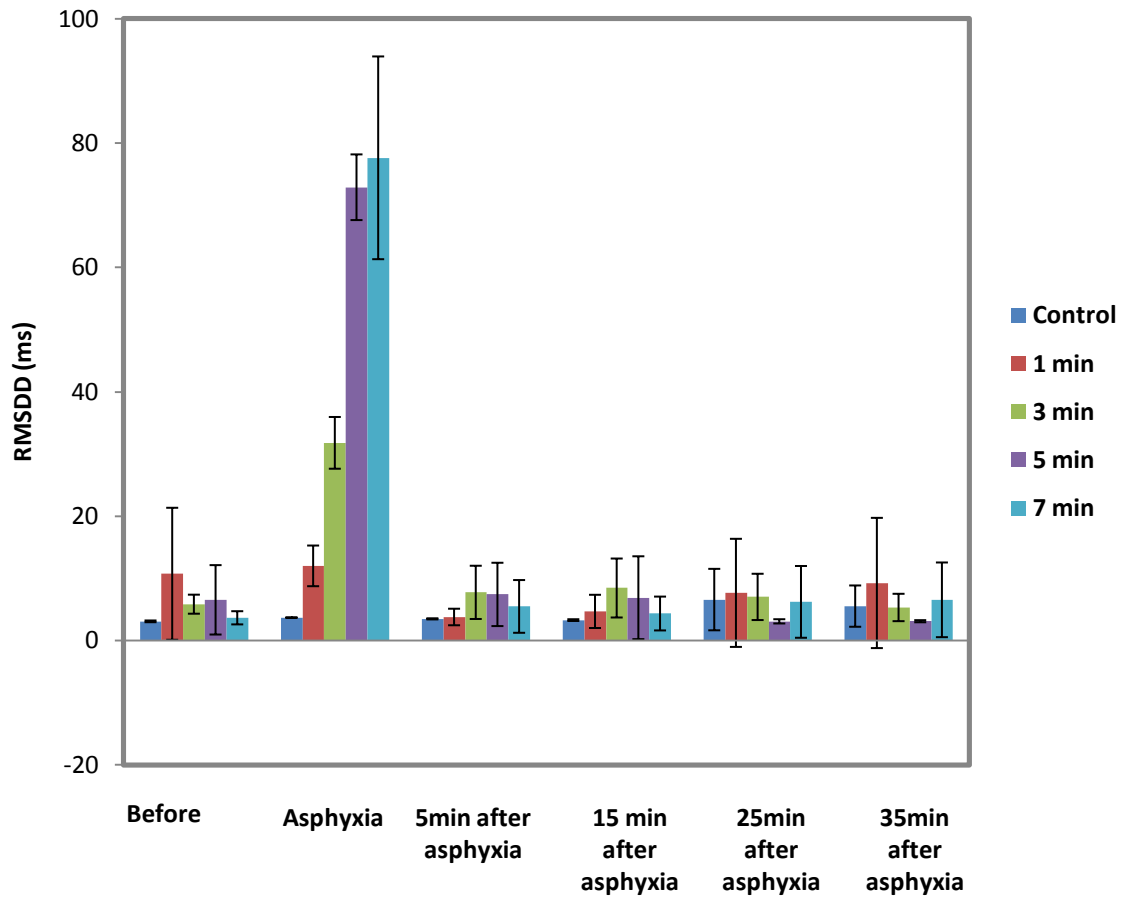


Figure 4. 4 RMSDD for the different groups of rats.

The RMSDD confirms that for the time domain indices the results are similar and present the same trend (Malik, 1995.), all of them were able to identify when the asphyxia was occurring, and presented the same tendency of a decrease after the insult.

4.3.2 Frequency Domain

The results of power spectral analysis using FFT and autoregressive model of order 20 are shown in table 4.1 and table 4.2.

Table 4. 1 Spectral analysis using FFT

FFT Power (normalised units)						
	LF		HF		LF/HF	
	Before	After	Before	After	Before	After
Control	1.6	24.9	98.4	75.1	0.01	0.33
1 min	9.92	4.1	90.07	95.9	0.11	0.04
3 min	9.7	27.73	90.3	72.26	0.1	0.38
5 min	27.66	1.83	72.33	98.17	0.38	0.01
7 min	34.13	8.43	65.86	91.56	0.51	0.09

Table 4. 2 Spectral analysis using autoregressive model of order 20.

AR (normalised units)						
	LF		HF		LF/HF	
	Before	After	Before	After	Before	After
Control	3.15	25.15	96.85	74.85	0.03	0.33
1 min	9.025	5.7	90.97	94.3	0.09	0.06
3 min	9.3	25.63	90.97	74.36	0.1	0.34
5 min	30.33	3.03	69.66	96.96	0.43	0.03
7 min	36.66	7.83	63.33	92.16	0.57	0.08

For the frequency domain methods we used a different approach, we focused in the analysis before and after the asphyxia to complement the results already obtained by time domain methods. We analysed the HF components (associated with parasympathetic activity and respiration modulation) and LF elements (reflecting the interplay of sympathetic and parasympathetic activity, (Malik, 1995.)). The obtained values for both methods presented a decrease, for the groups of 3 ,5 and 7 min. of asphyxia periods when comparing them before and after the insult occurred, however the trend for the mild asphyxia episodes of 1 min presented a different behaviour, indicating that this method is not be the best option to analyse short asphyxia episodes.

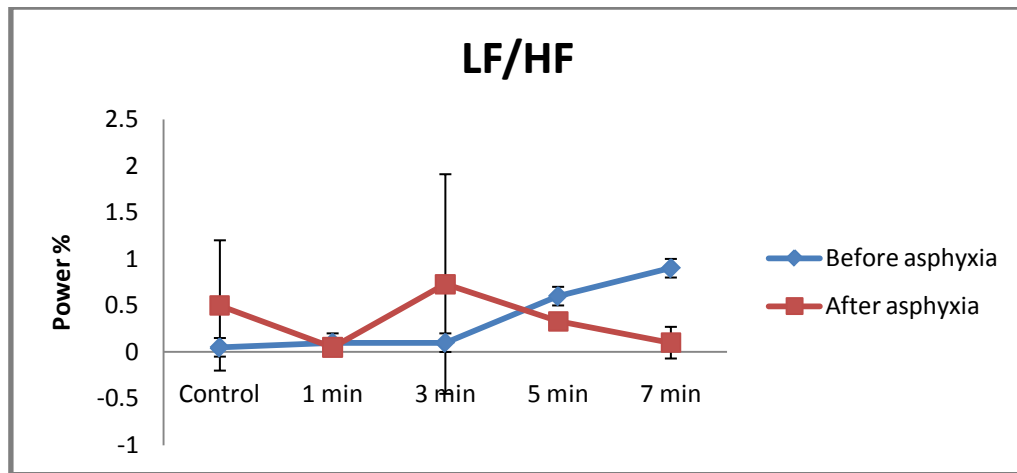


Figure 4. 5 Ratio of LF/HF expressed in power % obtained from the AR model

4.3.3 Poincaré Plots and indices

Through the use of the Poincaré plots we observed the different distributions of the RR points for the different groups of asphyxia (1,3,5,7 min), where the distance between the groups before and after asphyxia increased as the length of the asphyxia increased, this seems to reflect the severity of the insult. A typical result for one rat can be seen in Figs. 4.6-4.9, presenting the episodes before and after asphyxia.

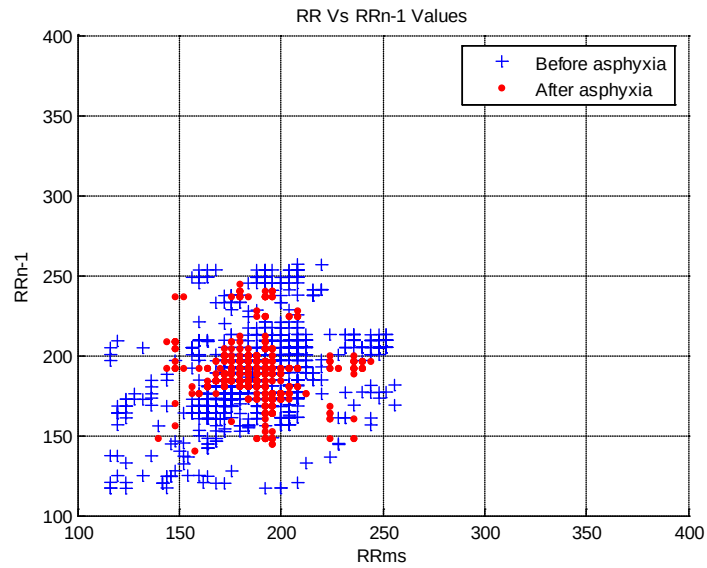


Figure 4. 6 Beat to beat distribution for 1 min of asphyxia.

The distribution of the points for one min of asphyxia is very similar, the clouds of points are in the same area of the plot, this agrees with the results obtained from the time domain and frequency domain methods where for 1 min of asphyxia the values are similar hinting that the injury seems to be no so severe.

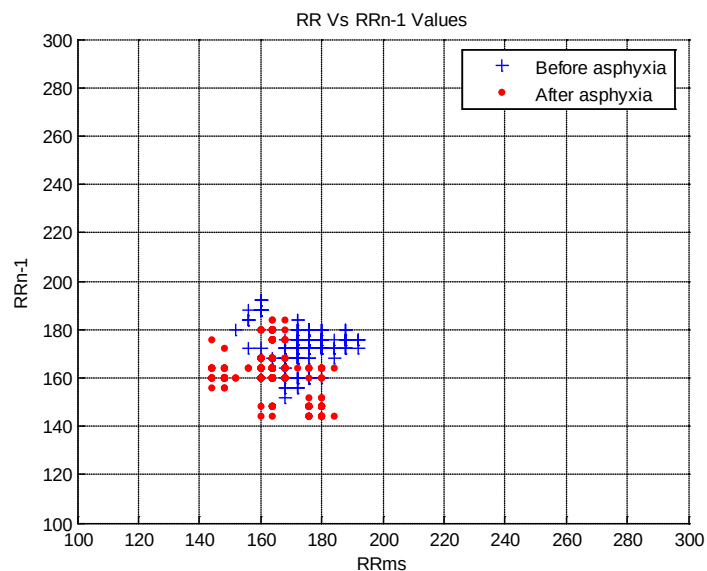


Figure 4. 7 Beat to beat distribution for 3 min of asphyxia.

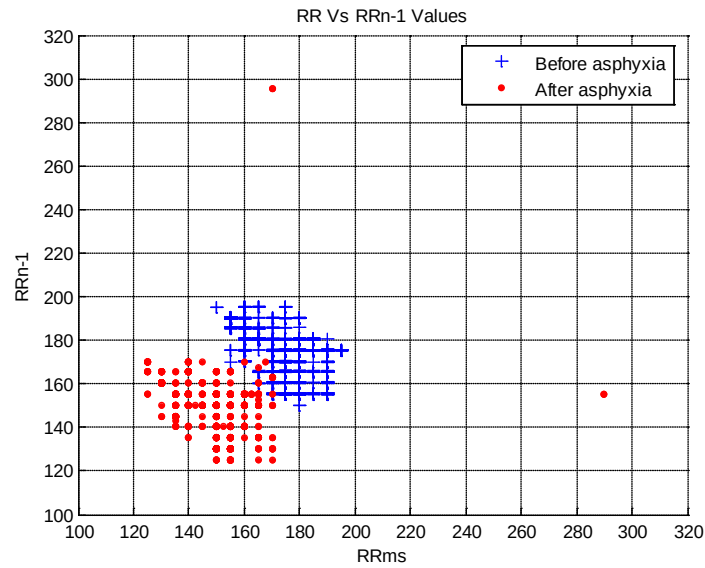


Figure 4. 8 Beat to beat distribution for 4 min of asphyxia.

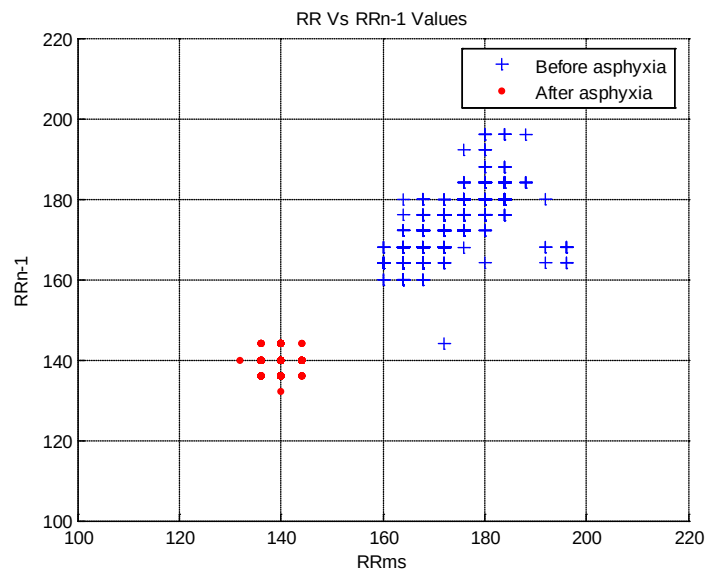


Figure 4. 9 Beat to beat distribution for 7 min of asphyxia.

The distribution of the beats for the rest of the experiments presented similar results for all the groups, where the clouds of points migrate apart on the plots as the asphyxia episodes get longer. From the visual analysis it is evident that these plots present a trend of behaviour for asphyxia episodes of different lengths, where the repetition of the value of the RR interval

gives the impression of a reduction in the number of points, due graphically there is a red point over another red point . In order to quantify the dispersion on these plots we obtained the indices SD1 (fig 4.10), SD2 (fig 4.11), CSI(fig 4.12) and CVI (fig 4.13).

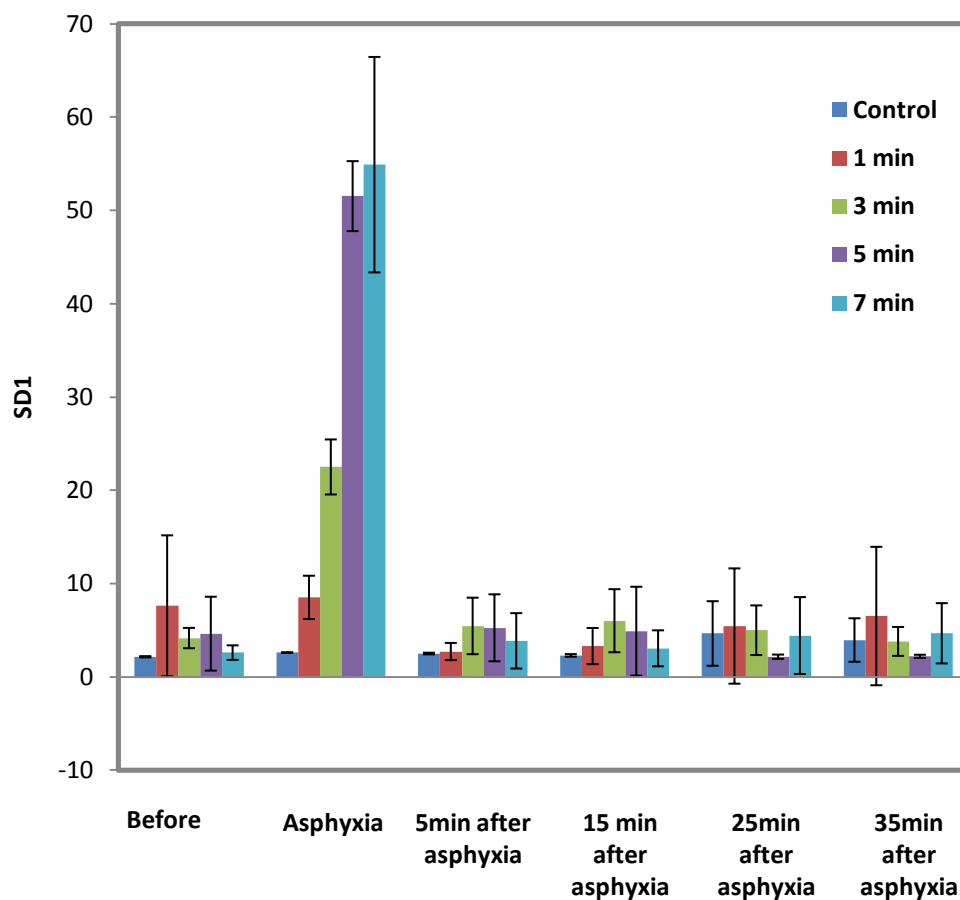


Figure 4. 10 SD1, short term beat to beat RR interval variability of all the groups, before and after asphyxia.

The analysis of the derived indexes from the Poincaré plots was completed using the same approach of the time domain indices, the short term variability is very sensitive to longer asphyxia periods with considerable increase during the insult.

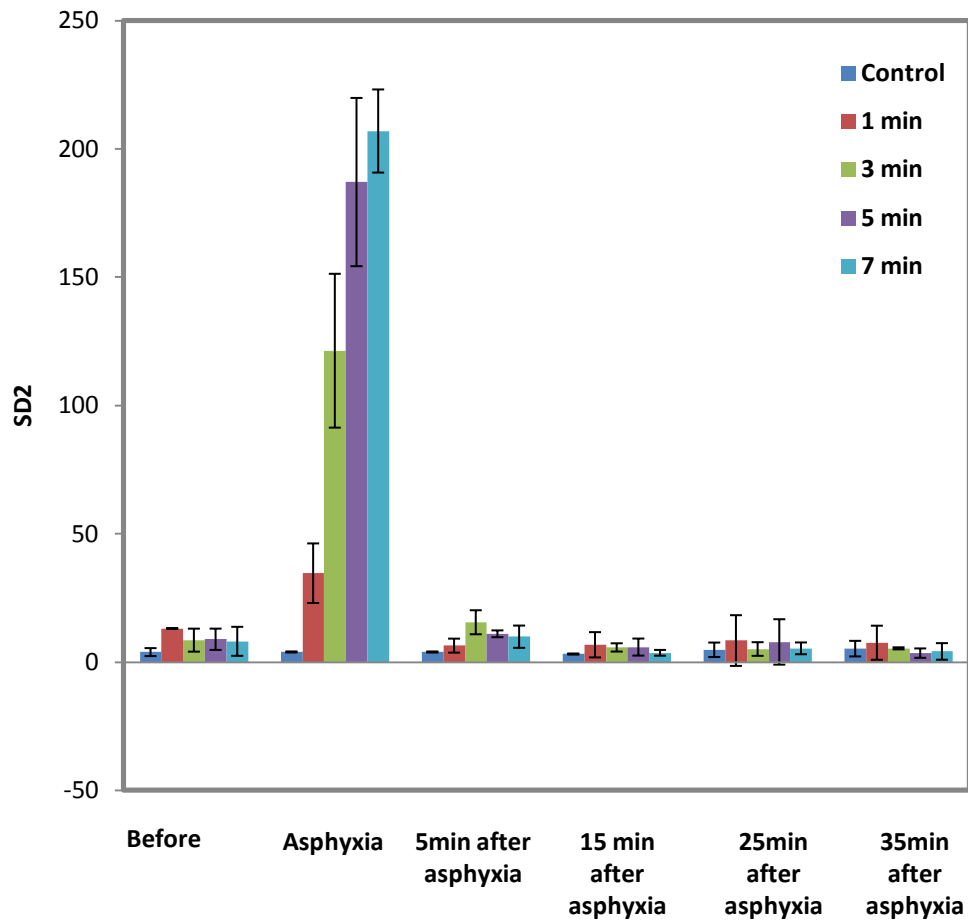


Figure 4. 11 SD2, long term beat to beat RR interval variability of all the groups, before and after asphyxia.

The long term variability analysis of the HRV obtained through SD2 presented, as SD1, an increase during the asphyxia but the reduction of its value after asphyxia was more pronounced in comparison to the other methods.

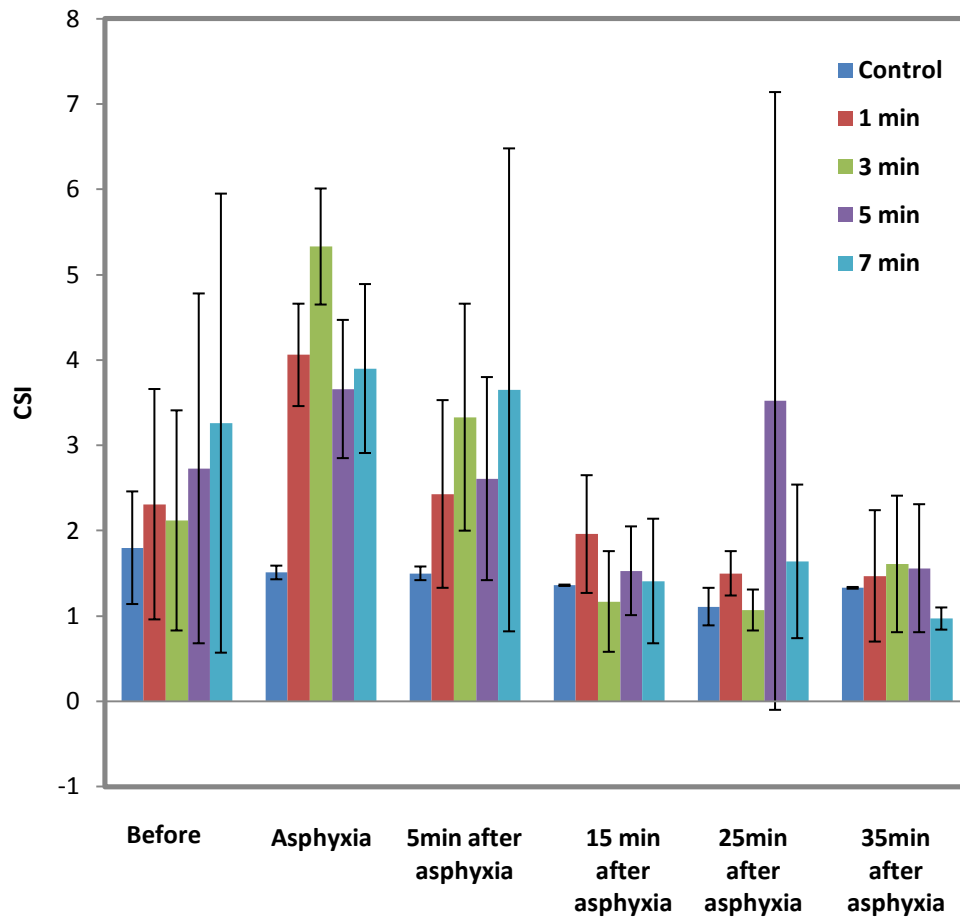


Figure 4. 12 Cardiac sympathetic index (CSI) before and after asphyxia.

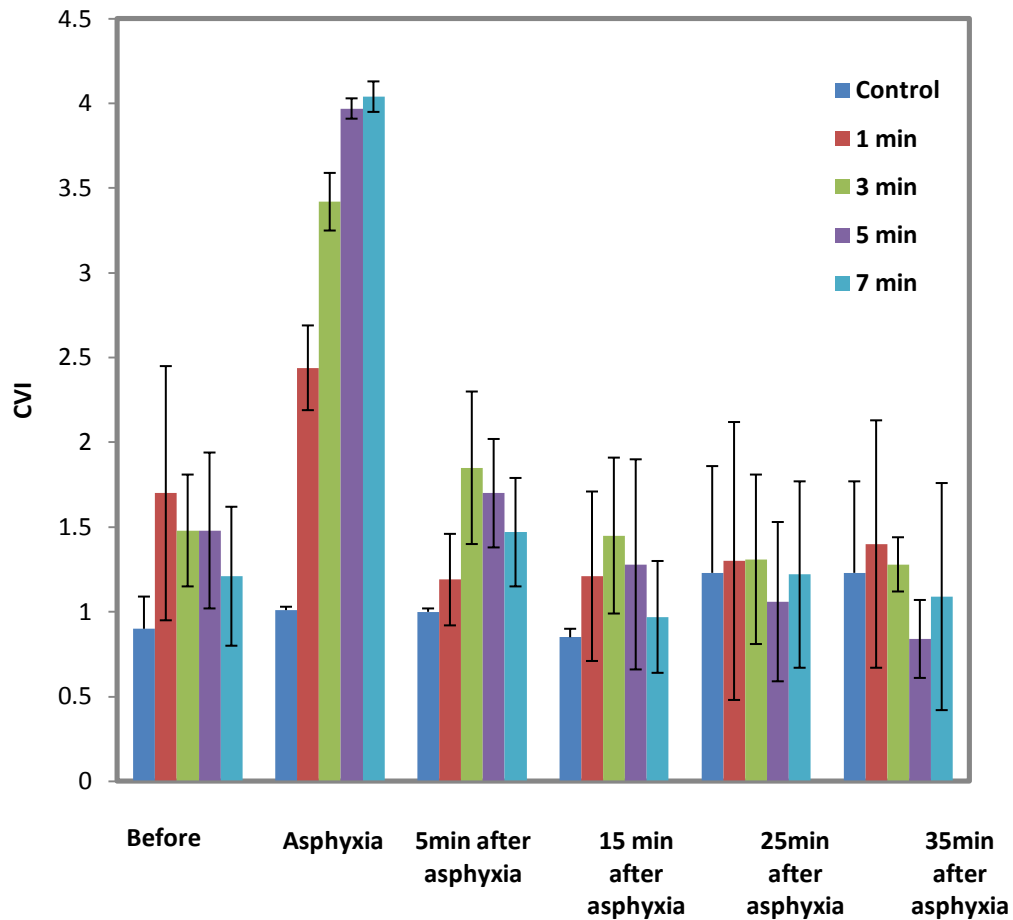


Figure 4. 13 Cardiac vagal index.

The cardiac sympathetic index and the cardiac vagal index, both of them reflected the induced asphyxia, but the changes in the value of the cardiac sympathetic index were more evident because is more sensitive to changes in the sympathetic-vagal balance.(Toichi et al., 1997). The large variability of Cardiac sympathetic index (figure 4.12) should be noted. It seems that the vagal activity is more affected by the asphyxia.

4.3.4 Complexity Indices.

The results obtained using approximation entropy and sample entropy are presented in figures 4.14, and 4.15.

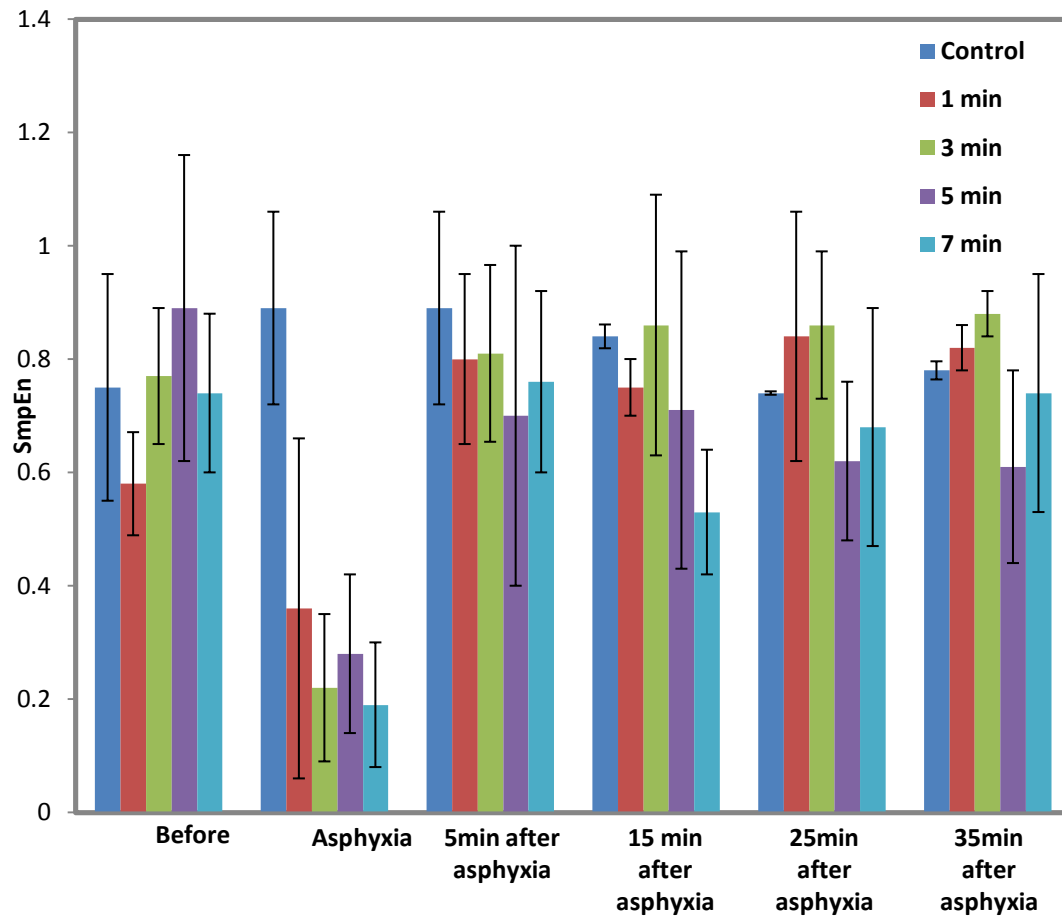


Figure 4. 14 Sample Entropy before and after asphyxia

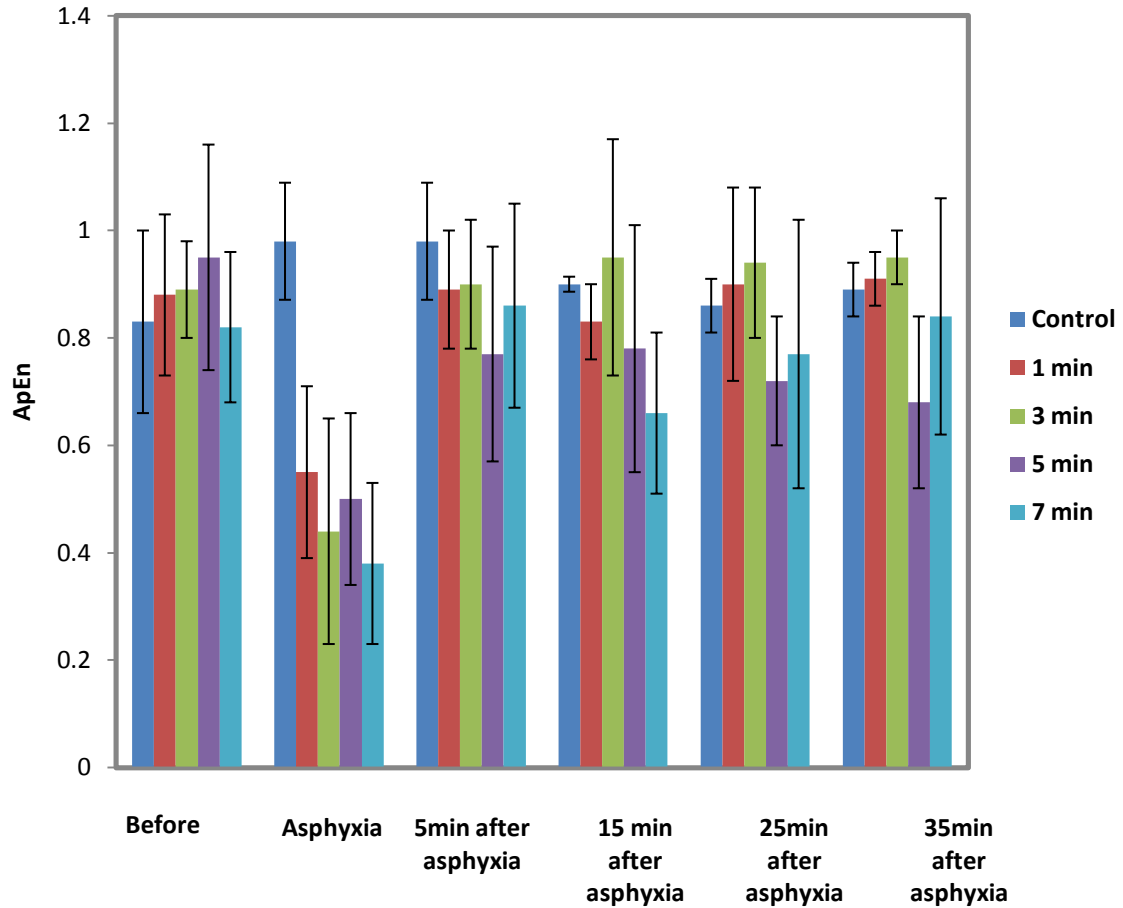


Figure 4. 15 Approximated entropy before and after asphyxia.

The value for both the entropy methods during the asphyxia episode decreased markedly, reflecting a reduction of the complexity of the signal. This result is in agreement with the description of a report of a large set of pathological conditions that are characterized by the loss of complexity of biological signals (Magesnes et al., 2003).

4.3.5 Detrended Fluctuation analysis

The detrended fluctuation analysis parameters α_1 and α_2 presented very interesting results. α_2 reflected the changes during asphyxia with a marked increase from the baseline value, particularly for the group of 1 min, α_2 seems to be more sensitive than α_1 to track the HRV changes for mild asphyxia episodes.

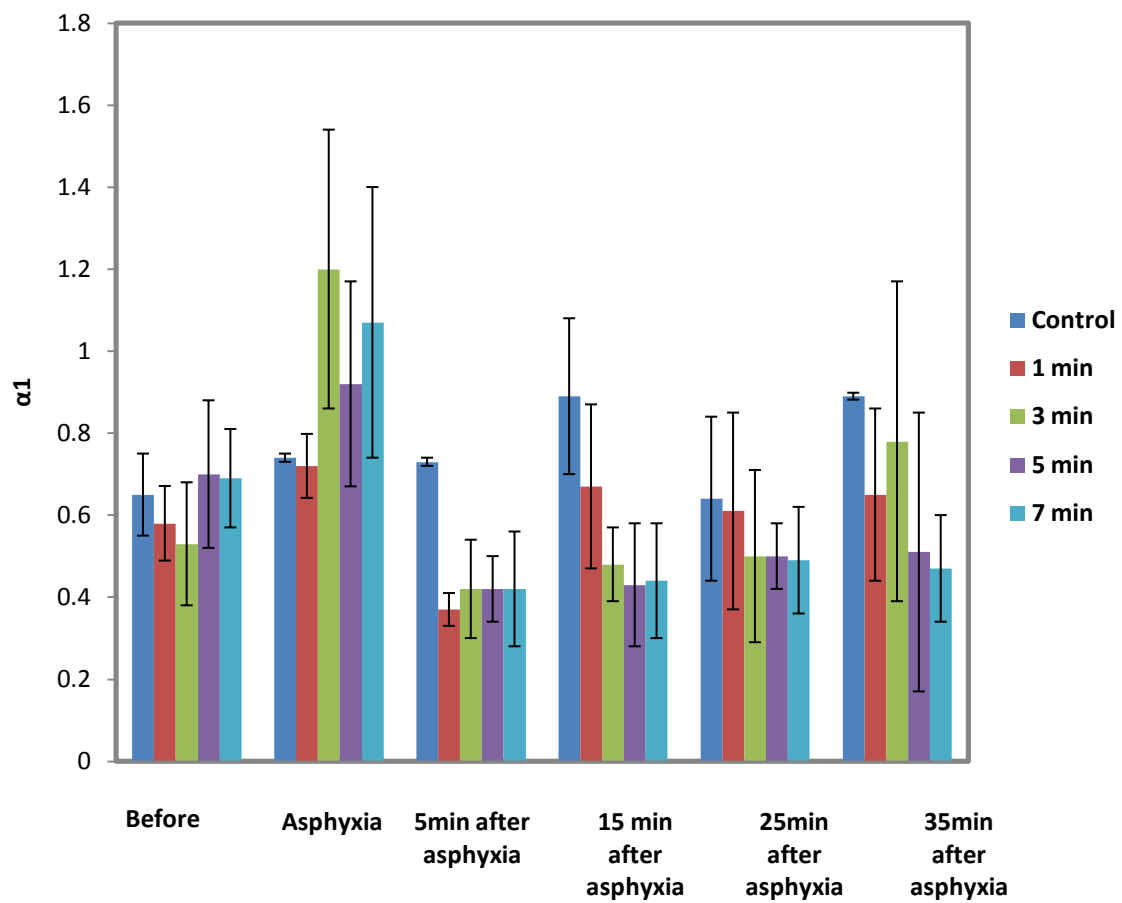


Figure 4. 16 Detrended fluctuation analysis α_1 .

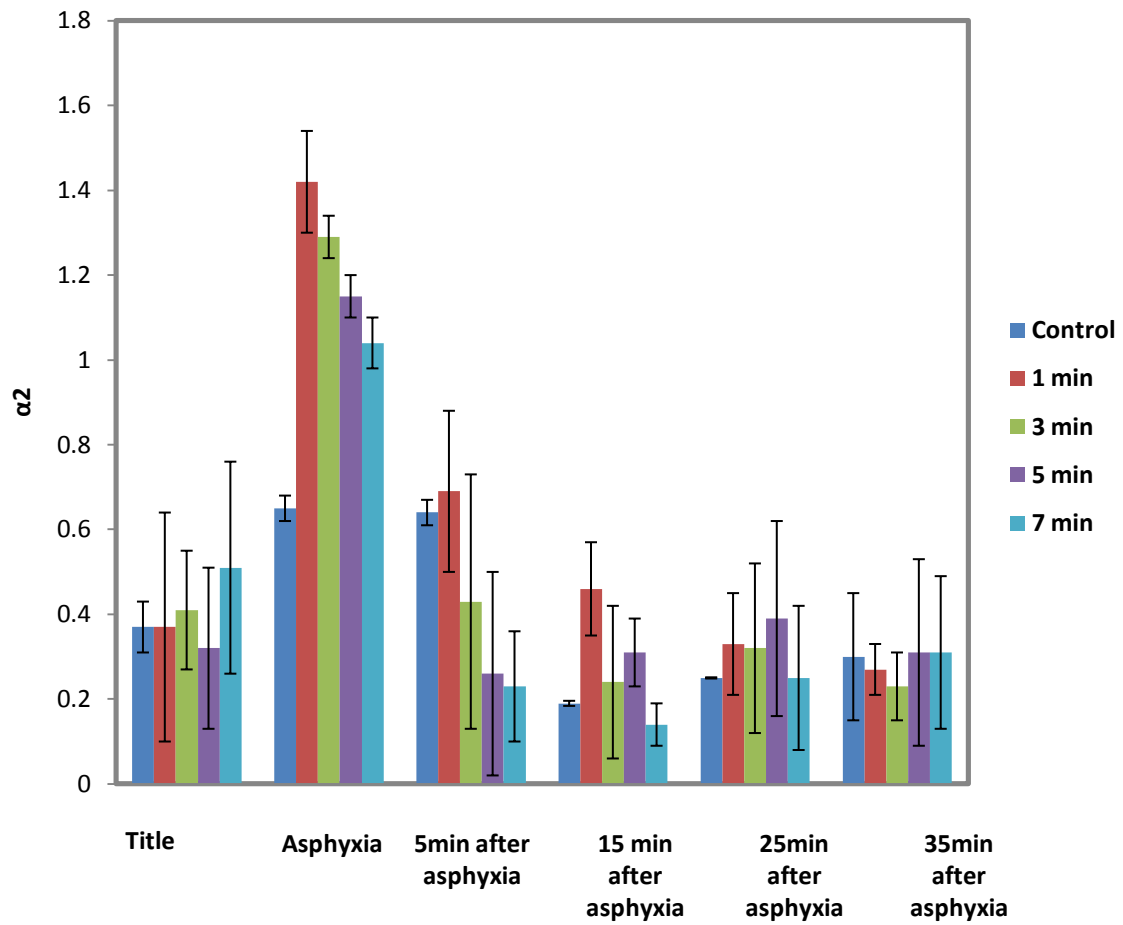


Figure 4. 17 Detrended fluctuation analysis α_2 .

A different trend for α_2 can be observed during the asphyxia episode for the group of 1 min, the increase in the value is more evident in comparison with the other groups.

4.4 Discussion.

In this study both linear and non-linear methods were used to obtain HRV measures before and after controlled asphyxia episodes, similar studies have also examined these measures but comparisons of the results obtained in the literature are difficult to make due to the different experiment protocols/methodology employed and the different values used for the spectral and the complexity analysis (Cai et al., 2006). Significant differences in the HRV values obtained before, during and after asphyxia were found.

Time domain and frequency domain methods have previously been used to describe changes in the HRV with the purpose of asphyxia detection in rats (Boardman, 2003) and to track of the HRV changes that occur after asphyxia (Moraru et al., 2004, Cai et al., 2006). Our study is different to most of these previous studies for the particular more complete combination of linear and non-linear methods applied. Using this combination of methods a more complete characterization of HRV can be achieved as behaviour that was not well detected using some of the techniques is highlighted by the use of other approaches.

Sixteen different time-domain, frequency-domain, complexity and Poincaré plots and indices were extracted from the RR time series. The time domain indices reflected in a very clear manner the occurrence of the asphyxia, and a combination of them allowed to monitor the changes along the different phases observed after the asphyxia.

From this more complete characterization we selected 8 indices, the ones that presented a meaningful difference of $p \leq 0.05$ to different asphyxia lengths in most cases, hence for our experiment they represent the optimal sub-set of parameters for characterizing the HRV. They are described from figure 4.18 to figure 4.21.

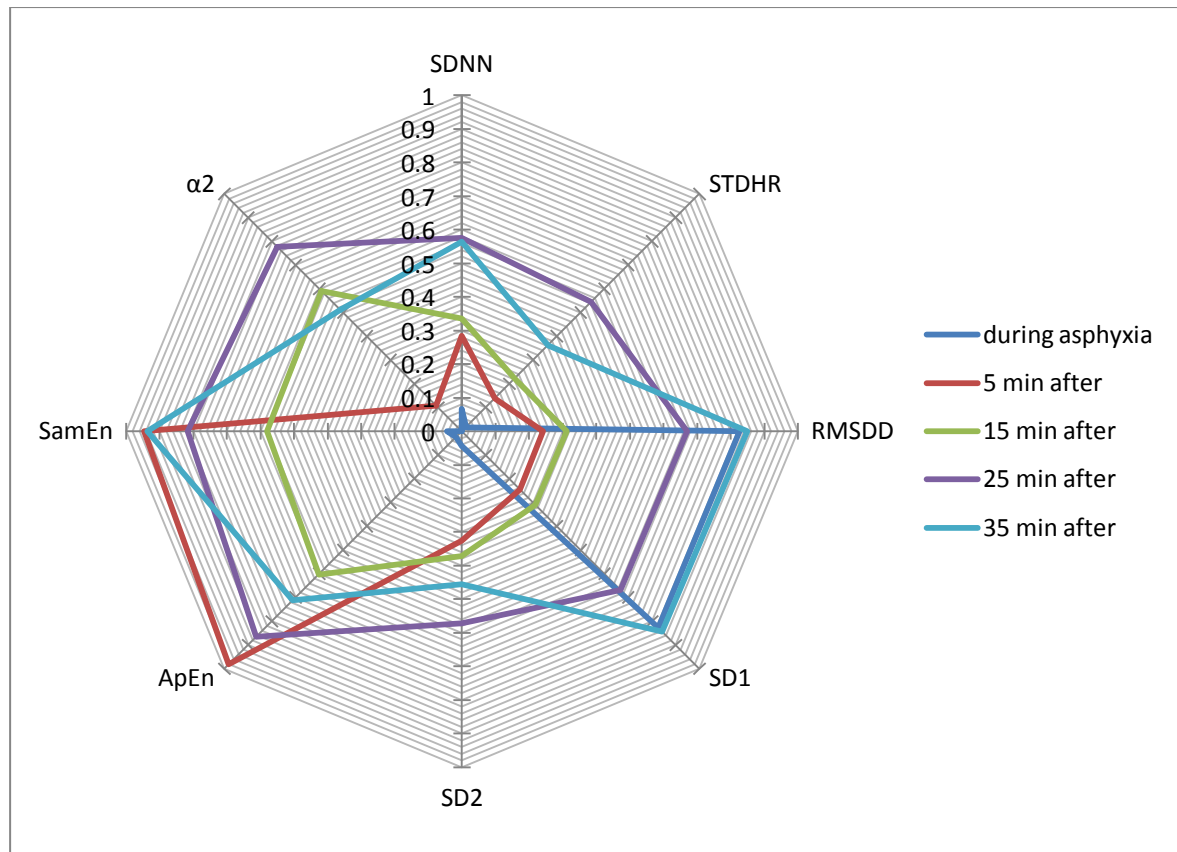


Figure 4. 18 Radar graph representation of the selected parameters that better reflected the changes before and after 1 min of asphyxia.

For the asphyxia length of 1 min., the indices that better reflected the changes due to the insult were α_2 and SDNN. After 5 min of asphyxia the changes were better tracked by the use of α_2 , SDNN, SD2, STDHR, SD1 and RMSDD. After 15 min the optimal methods were SDNN, STDHR, RMSDD, SD1 and SD2, after 25 min SD1, SD2, RMSDD, STDHR, finally after 35 min STDHR and SD2.

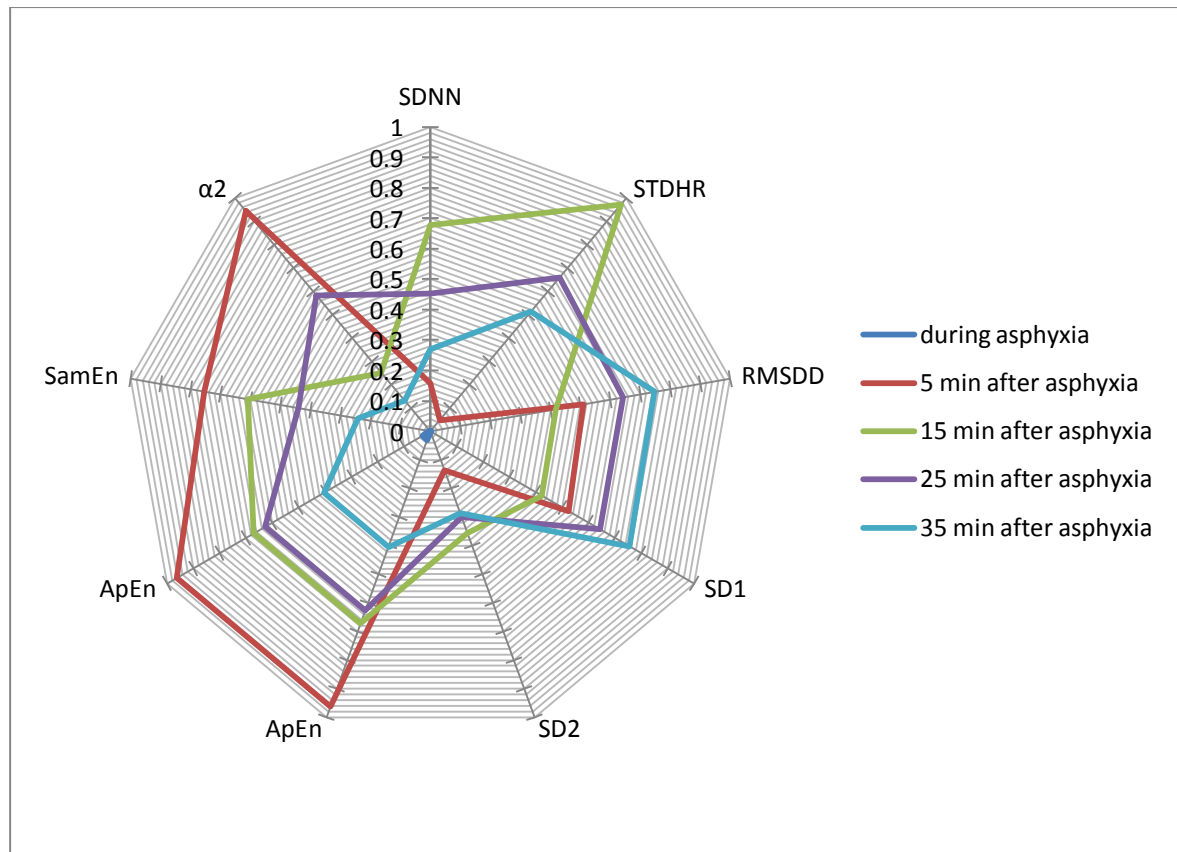


Figure 4. 19 Radar graph representation of the selected parameters that better reflected the changes before and after 3 min of asphyxia.

For the group of 3 min. of asphyxia, during the insult the indices that better reflected changes due to the lack of oxygen were, $\alpha 2$, SDNN, ApEN, SD1, RMSDD, STDHR, SamEn and SD1, presenting a robust detection. After 5 min of asphyxia STDHR, SD2 presented the most significant changes, after 15 min it was $\alpha 2$; after 25 min SD2, $\alpha 2$ and SamEn, and finally, after 35 min., $\alpha 2$, SD2, SamEn, ApEn.

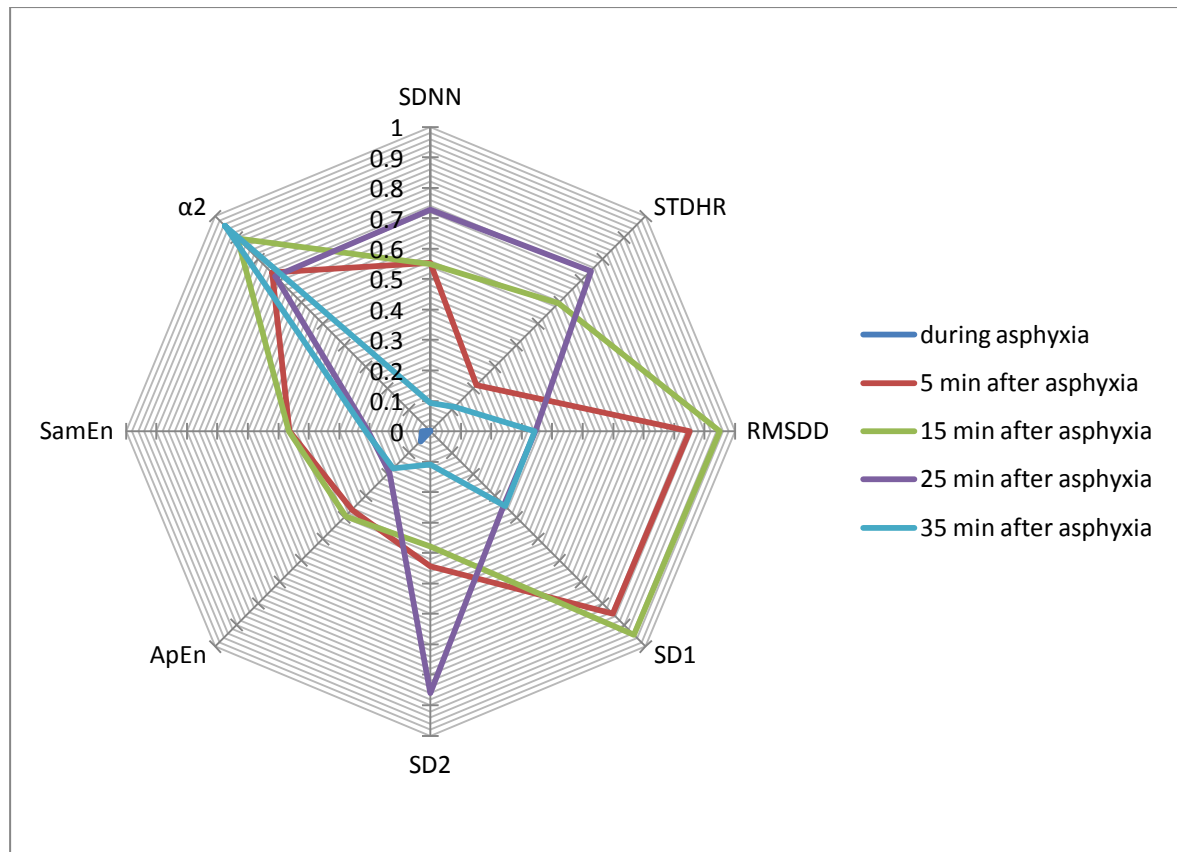


Figure 4. 20 Radar graph representation of the selected parameters that better reflected the changes before and after 5 min of asphyxia.

For the group of 5 min of asphyxia, during the insult the indices that better reflected more changes due to the lack of oxygen were α_2 , SDNN, ApEn, SD1, RMSDD, STDHR, SamEn and SD1. After 5 min of asphyxia the STDHR presented the most significant changes; after 15 min the best indices were the SamEn , ApEn and SD2. After 35 min of asphyxia SDNN, SD2, ApEn, SamEn and STDHR presented more changes than the other indices.

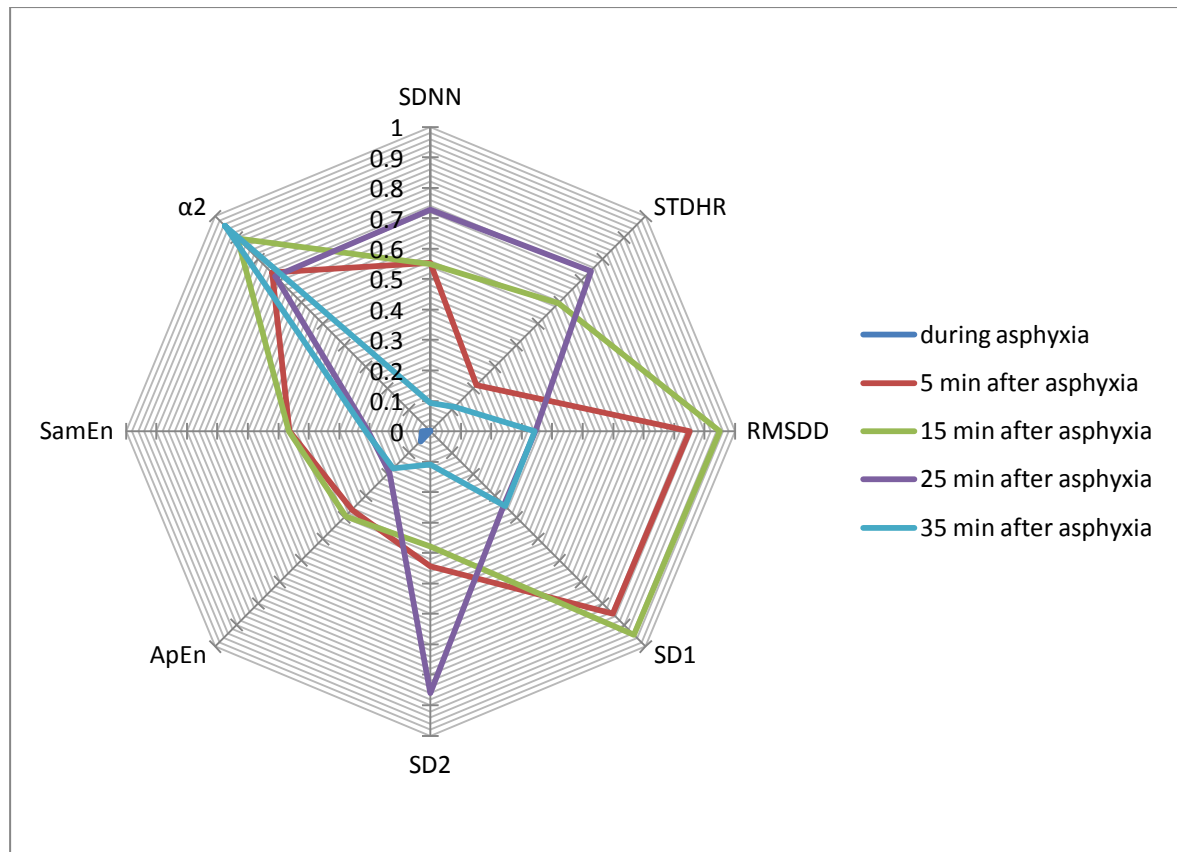


Figure 4. 21 Radar graph representation of the selected parameters that better reflected the changes before and after 7 min of asphyxia.

For the group of 7 min of asphyxia, during the insult the indices that better reflected more changes due to the lack of oxygen were α_2 , SDNN, ApEn, SD1, RMSDD, STDHR, SamEn and SD1. After 5 min of asphyxia STDHR reflected more significant differences it respect to the other techniques, after 15 min and 25 min the best methods were ApEn and SamEn, and finally, after 35 min, ApEn, SamEn, SD2 and SDNN were the most specific.

The radar graphs summarize, for all the groups, the most significant results of the comparisons before, during and after the asphyxia episodes, where the combination of linear and non-linear parameters monitored the changes occurred along time in the HRV. The selected 8 methods reflected in a robust manner the changes along the different asphyxia episodes.

Unfortunately the recording of the experiment didn't last for much longer after the asphyxia was been induced. We were interested in this because the values obtained to measure approximated entropy started to increase after the injury and it has been reported that this could reflect the transition to a possible pathological condition, with an increase in the irregularity and uncorrelated randomness in the pattern of the HR signal (Magesnes et al., 2003). We think that this could represent a marker to assess the severity of the injury.

4.5 Conclusions.

The analysis of the HRV using different parameters has shown that some of the methods are more sensitive to the degree of asphyxia, with the majority of the parameters obtained presenting the same tendency of decrease with the severity of the asphyxia. To assess the amount of injury suffered and to validate the feasibility of using our proposed cluster of selected methods to assess fetal asphyxia/hypoxia it would be necessary to obtain records of longer duration after the induced asphyxia. The use of the complete set of indices and methods that we have implemented represents a novel contribution towards the detection and classification of asphyxia.

Our results reflected changes in parameters before, during and after asphyxia. The proposed combination of techniques provides a variety of information that might help clinical staff to reduce the mortality and morbidity of asphyxia-related incidents. The next step will be to implement these techniques for the study of RR time series extracted from human fetal data, and try to corroborate our findings. Some steps in this direction are described and commented in the next chapter.

Chapter 5

Analysis of fetal HRV during labour

“Do not go where the path may lead, go instead where there is no path and leave a trail”

Ralph W. Emerson

5.1 Introduction.

In this chapter, we describe a complete HRV analysis performed on the beat-to-beat intervals extracted from Doppler ultrasound using time domain, frequency domain and non-linear Poincaré indices. Then we compare this results with HRV analysis of beat-to-beat intervals extracted from fetal scalp ECG of same time interval as a gold standard.

An optimal filtering followed by adaptive thresholding method was applied to extract the beat-to-beat interval of the heart using the scalp fetal ECG (Boardman et al., 2002b, Schlindwein et al., 2006). The beat-to-beat intervals of the heart rate for Doppler audio envelope signals were extracted using autocorrelation function, wavelet transform and Hilbert-Huang transform. To finish we present our results, where the beat-to-beat intervals extracted using autocorrelation from Doppler envelope signals correlate well with the beat-to-beat intervals obtained using the scalp fetal ECG. Finally HRV analysis was performed on the beat-to-beat intervals extracted from both Doppler envelope signal and scalp fetal ECG. HRV indices computed from the Doppler envelope strongly agree with those computed from scalp FEKG.

5.2 Data acquisition and beat-to-beat heart rate detection.

Using a HP8040A monitor, four signals, scalp fetal ECG, Doppler audio envelope, raw Doppler ultrasound and uterine contractions (TOCO) were collected at 2000 samples per second (Schlindwein et al., 2004). In the present study we used the scalp fetal ECG and Doppler audio envelope signals as shown in figure 5.1. We used the Doppler audio envelope signal because the envelope delivered from the fetal monitor is a good match of the envelope calculated from the spectral analysis of the raw Doppler signal (Boardman, 2003).

We analysed a data set containing 520 heart beats extracted from the scalp FECG and Doppler audio envelope. The performed study is described.

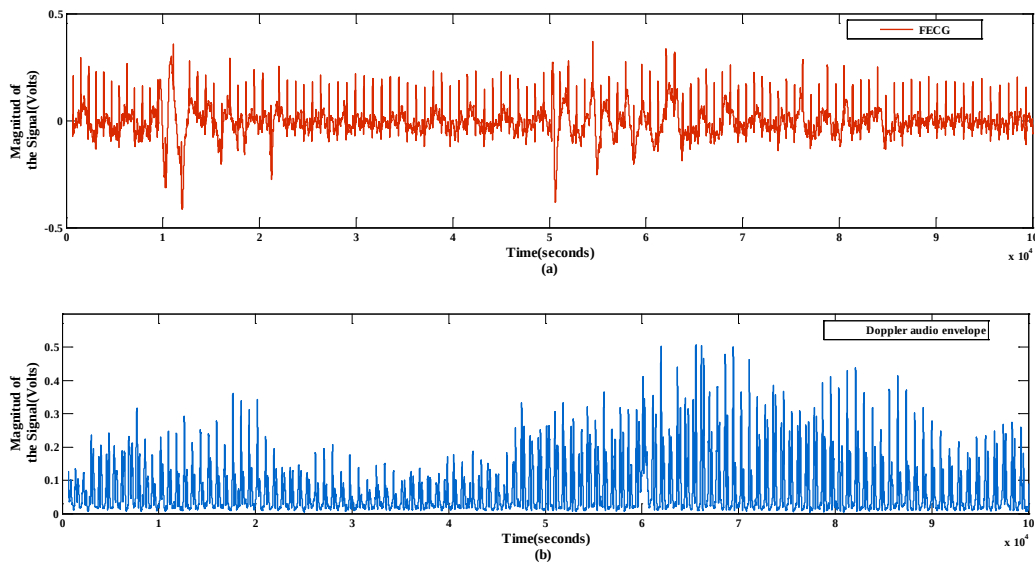


Figure 5. 1 Data obtained from the HP8040A monitor: a) Scalp fetal ECG, b) Doppler audio envelope

5.2.1 Extraction of beat-to-beat intervals from FECG

After applying a second order Butterworth band pass digital filter with cut-off frequencies of 5 and 36 Hz, adaptive thresholding technique was employed for R peak detection (Boardman et al., 2002b). The adaptive threshold was heuristically adjusted and tended to 65% of the running average of the magnitude of the R peak. A refractory period of 112 ms was used to reduce the possibility of false positive detections.

5.2.2 Extraction of beat-to-beat intervals from Doppler envelope

Autocorrelation Function

Auto-correlation has a unique feature to represent the periodicity of signals (Weiner, 1930), as it results in an adaptive matched filter. At the core the auto-correlation function of a signal is a means of measuring the correlation of a function with its past, present and future values (Stearns and Hush, 1990). The beat-to-beat interval extraction involves two steps. In the first step fiducial points from the Doppler audio envelope were determined to identify individual heart beats. This was achieved by using a low-pass filter with a cut-off frequency of 4 Hz to the Doppler audio envelope signal from where we located the maxima of each cycle (Voicu et al., 2010). For the second step we used the autocorrelation in frequency domain. For the detection of the beat-to-beat intervals we set up a sliding window to shift the signal and compare it to a delayed version of itself (2 seconds-long windows produced the best detections). We found the places at where the signal was more similar, pointed by the highest correlation value. The calculation of the heart rate was estimated computing the time distances between consecutive positions of the maxima of the autocorrelated signal (Voicu et al., 2010).

Wavelet analysis of the Doppler envelope

The time/frequency analysis capabilities offered by the Wavelet Transform made it become a powerful tool for the analysis of non stationary signals. This approach is based on functions that split the data into different frequency components, and allows the study of each component with a resolution matched to its scale (Daubechies, 1992). We use the discrete wavelet ‘Coif5’ at level 9 to decompose the Doppler audio envelope into coefficients that can were associated with different scales and times. By taking 87 values of the approximation coefficient to perform data reconstruction, a signal with an approximate sinusoidal behaviour was obtained and the maxima of each cycle can be easily identified allowing the estimation of the heart beat intervals from the distances between them.

Hilbert-Huang transform analysis of the Doppler envelope

The Hilbert-Huang Transform (HHT) is a relatively new technique introduced by Huang *et al.* 1996 to analyse non-linear and non-stationary time series. The Hilbert-Huang Transform comprises of two parts: the empirical mode decomposition (EMD) and Hilbert spectral analysis (Huang et al., 1998).

The core of this method is the identification of the intrinsic oscillatory modes by their unique time scales in the data empirically, and then the decomposition of the data accordingly (Huang et al., 1998).

EMD was used to extract the intrinsic mode functions (IMF) of the Doppler audio envelope signal, the signal was reconstructed by taking the 8 first IMF, presented an approximately sinusoidal shape from which the maxima of each bump was calculated, and the heart rate calculated from the distance between them.

5.2.3 Heart rate variability analysis

Heart rate variability analysis was performed using: Time domain (mean RR, SDNN, STDHR and RMSDD), frequency domain where the power spectral analysis was performed using parametric method autoregressive (AR) modelling. The AR spectrum yields improved resolution especially for short sample lengths. Secondly the AR spectrum can be factorized into separate spectral components and this property has made it popular in HRV analysis. Prior to power spectral density estimation, the RR-interval time series was converted into equidistantly sampled time series using cubic spline interpolation. The power spectral indices for HRV analysis included low frequency LF (0.04-0.15 Hz), high frequency HF (0.15-0.4 Hz) and ratio of LF to HF power (LF/HF). And also Poincaré plot indices (SD1, SD2, CSI, CVI) at different lags.

5.3 Results.

5.3.1 Beat-to-beat interval detection

In figure 5.2, the results of beat-to-beat intervals extracted from the scalp FECG as a reference signal and beat-to-beat intervals extracted from Doppler envelope signals by using three methods (Autocorrelation function, Wavelet transform and Hilbert-Huang transform) are shown. Analyzing the original waveform of the Doppler Ultrasound signal (figure 5.1(b)), a considerable

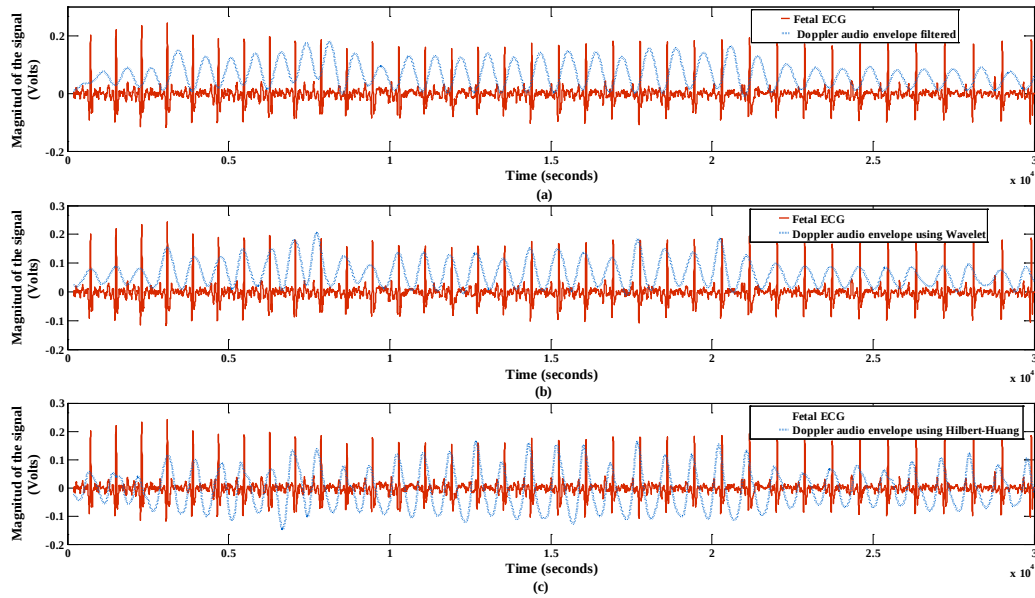


Figure 5. 2 Scalp fetal ECG superimposed to the Doppler audio envelope after being processed by the three proposed methods: a) Autocorrelation (this signal corresponds to the filtered part of the method). b) Wavelet Transform. c) Hilbert-Huang Transform.

Improvement has been achieved after processing it by the suggested methods. Visually the individual beats now could be easily identified.

The difference of beats detected from fetal scalp FECG and beats detected from Doppler audio envelope signals by the three methods was calculated using the relation error differences, where N_{FECG} Beat-to-beat detections from the scalp FECG, and

Beat-to-beat detections from the Doppler audio envelope from each method. The beat-to-beat intervals extracted from Doppler audio envelope signal using Autocorrelation were in good agreement with beat-to-beat intervals, extracted from FECG (up to ± 5 ms) whereas the other two methods computed differences were up to ± 150 ms for the Wavelet Transform and up to ± 210 ms for the Hilbert-Huang Transform. The plot of the FHR shows that Wavelet and Hilbert-Huang transforms methods are capable of determining the beats with enough precision to compute the average heart rate.

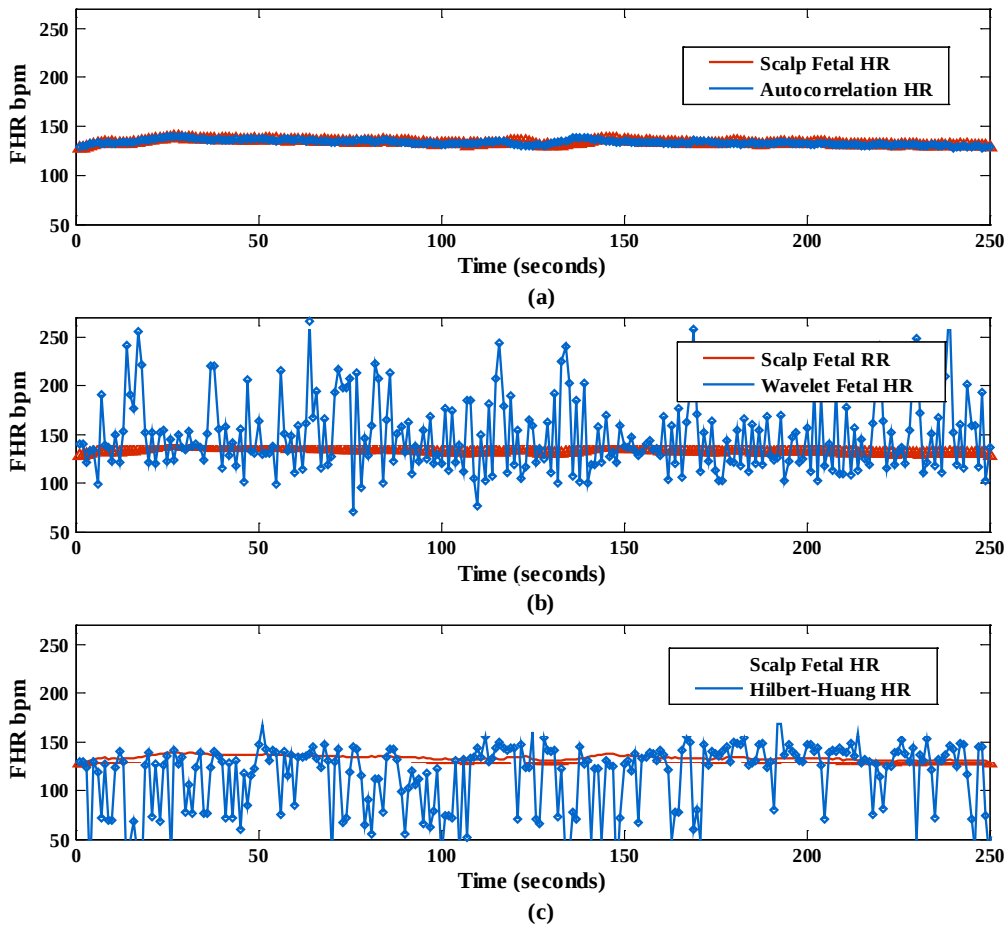


Figure 5.3 Comparison of fetal heart rate (HR) extracted from fetal ECG signals and fetal heart rate extracted from Doppler audio envelope signals by using three methods: (a) Autocorrelation function, (b) Wavelet transform, (c) Hilbert-Huang transform

Nevertheless there are large errors in the detection of the fiducial point for individual beats. (Figures 5.4 (b) and (c)). It is clear from figure 5.3(a) that fetal heart rate extracted from Doppler audio envelope signal showed an almost perfect match with fetal heart rate extracted from scalp FECG, whereas fetal heart extracted by Wavelet Transform and Hilbert-Huang Transform (figure 5.3 (b-c)) showed a larger disagreement with the heart rate extracted from the scalp FECG. The heart rate extracted from scalp FECG is plotted against the heart rate determined from Doppler envelope signals using: Autocorrelation function, Wavelet transform and Hilbert-Huang transform. A linear regression model was fitted to visualize and measure the closeness (strength) of the obtained heart rate to that using FECG as shown in figure 5.4. The pattern of points for all three

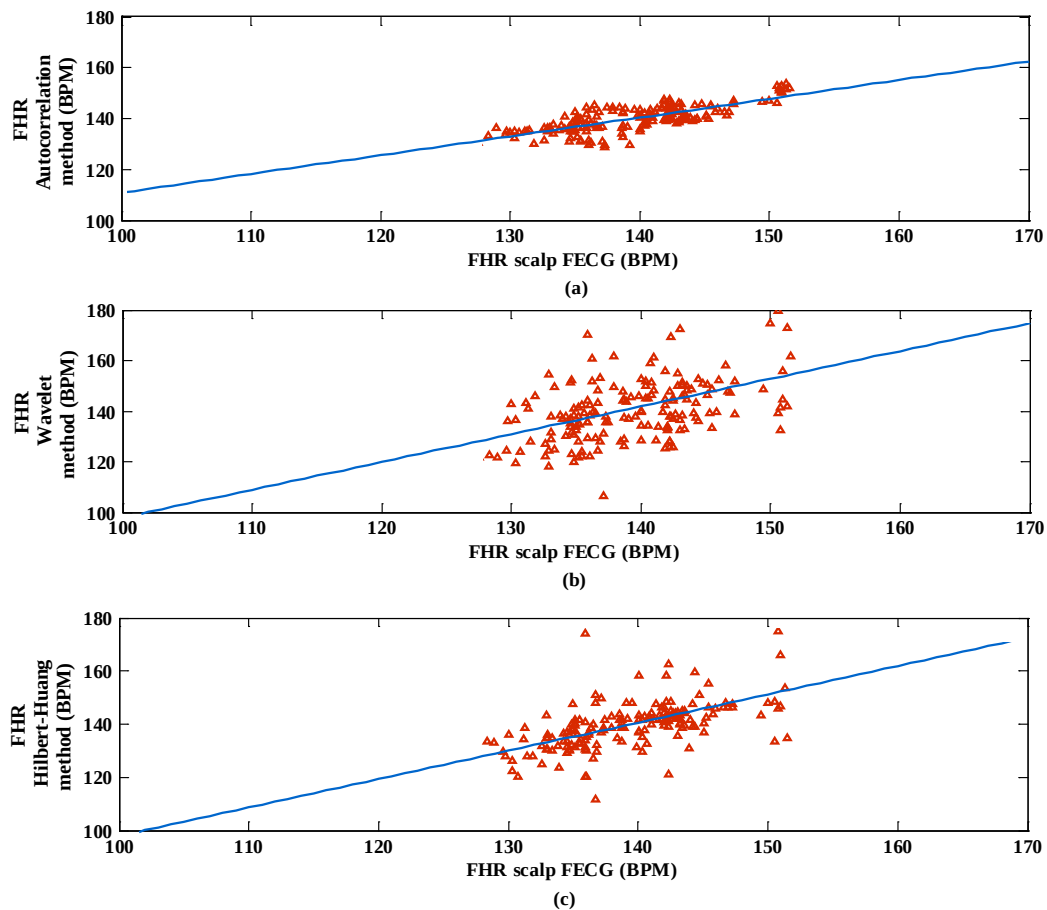


Figure 5. 4 Linear regression of the beat intervals obtained by the three techniques and the beat intervals obtained from the FECG. (a) Autocorrelation, (b) Wavelet Transform and (c) Hilbert-Huang Transform.

Techniques follows the identity line, with the least dispersion for the autocorrelation approach. The correlation coefficient for the heart rate determined from scalp FECG and heart rate determined from Doppler audio envelope using the three methods are listed in table 5.1. The highest correlation for heart rate determined from scalp FECG signal was found with heart rate obtained from Doppler envelope signal using autocorrelation method.

Table5.1. Correlation coefficient of the heart rate determined from scalp FECG and heart rate determined by Doppler audio envelope using: Autocorrelation function, Wavelet transform and Hilbert-Huang transform

Method	Correlation Coefficient
Autocorrelation	0.94
Wavelet Transform	0.73
Hilbert-Huang Transform	0.50

The correlation coefficient obtained from the beat-to-beat interval detection using the Wavelet transform method and the scalp FECG was $r=0.73$, which is worse than that obtained from the autocorrelation method. From the results obtained the autocorrelation method is the only one, out of the three tested, with acceptable results, with the Wavelet method in second place and the Hilbert Huang in third. Since one of the long terms goals of this research is the use in real-time, we calculated the computing effort required by each method. For 520 heartbeats analysed, the fastest method to find the beat-to-beat intervals was

the one based on the Wavelet Transform (0.032 sec), and the one that took more computing time was the one based on the Autocorrelation function (0.096 sec). The precision in the detections achieved by the Autocorrelation method is related to an increase in the computational requirement in comparison with the other two methods

5.3.2 HRV Analysis

Heart rate extracted from Doppler audio envelope signals using autocorrelation method was in good agreement with heart rate extracted from scalp FECG signal. Hence heart rate variability analysis was performed using beat-to-beat intervals extracted from Doppler audio envelope using autocorrelation and results were compared with beat-to-beat interval extracted from scalp FECG. The values of HRV time domain measures for scalp FECG and Doppler audio envelope beat-to-beat intervals are presented in table 5.2.

Table 5.2. Time Domain Indices.

	MEANRR (ms)	SDNN (ms)	MEAN HR (1/min)	STD HR (1/min)	RMSDD (ms)
Scalp FECG	435.38	17.29	138.04	5.53	3.60
Doppler audio Envelope	436.61	17.65	137.66	5.60	4.19
Difference	1.23	0.36	0.38	0.07	0.59

The results of power spectral analysis using autoregressive model of order 20 are shown in table 5.3. The values of LF, HF are given in normalized units.

Table 5.3. Spectral Analysis using Autoregressive model of order 20.

	AR (n.u.)		
	LF	HF	LF/HF
Scalp FECG	83.0	17.0	4.8
Doppler audio envelope	83.8	16.2	5.1
Difference	0.8	0.8	0.3

The results of indices SD1, SD2, CVI and CSI from Poincaré plots at lags (1-6) are shown in table 4. It is clear from table 5.4 that the four indices are very similar for scalp FECG and Doppler envelope signal.

Table5.4. Poincaré Indices at Different Lags

SD1(ms)						
	Lag1	Lag2	Lag3	Lag4	Lag5	Lag6
Scalp FECG	3.53	4.49	5.53	6.58	7.51	8.36
Doppler audio envelope	3.54	5.24	6.22	7.009	7.74	8.43
Difference	0.01	0.75	0.69	0.42	0.23	0.07
SD2(ms)						
Scalp FECG	22.80	22.63	22.40	22.11	21.82	21.50
Doppler audio envelope	22.67	22.34	22.08	21.80	21.64	21.34
Difference	0.13	0.29	0.32	0.31	0.18	0.16
CSI						
Scalp FECG	6.45	5.04	4.05	3.36	2.90	2.57
Doppler audio envelope	6.40	4.26	3.54	3.11	2.79	2.53
Difference	0.05	0.78	0.51	0.25	0.11	0.04
CVI						
Scalp FECG	1.905	2.007	2.09	2.16	2.21	2.27
Doppler audio envelope	1.904	2.06	2.13	2.18	2.22	2.25
Difference	0.001	0.053	0.04	0.02	0.01	0.02

5.4 Discussion.

The beat-to-beat intervals were extracted from the Doppler audio envelope signal using Autocorrelation, Wavelet transform and Hilbert-Huang transform methods. Linear regression analysis and Bland-Altman plots showed that beat-to-beat detections determined from Doppler audio envelope signal using autocorrelation method is consistent with beat-to-beat detections determined from scalp FECG. Beat-to-beat intervals determined from Doppler audio envelope signal using Wavelet and Hilbert Huang methods showed disagreements with beat-to-beat detections determined from scalp FECG.

The intrinsic adaptive property of the autocorrelation technique allowed a very good beat-to-beat heart interval detection using a sliding window of 2s length. Since the normal fetal heart rate is between 110 to 160 bpm, the lags of the Autocorrelation function were set-up to allow detection for a wider range of heart rates, between 80 to 200 bpm.

The beat interval detection from the Doppler envelope using Wavelet transform and Hilbert-Huang transform presented large jitters compared to the values obtained from FECG due to the fact that the values of the coefficients for the wavelet transform and the intrinsic mode functions for the Hilbert-Huang transform are global, i.e., they are defined using the whole signal. Heart rate variability analysis was performed using time domain, frequency domain and Poincaré indices, after extracting beat-to-beat intervals from scalp FECG and Doppler audio envelope signal using autocorrelation method.

The HRV indices calculated from beat-to-beat intervals of Doppler audio envelope signal corresponded well with HRV indices calculated from RR-Interval time extracted from scalp FECG, justifying that approach for assessing physiological state of fetus health non-invasively.

5.5 Conclusions.

This study performed a heart rate variability analysis of the Doppler audio envelope signal collected during labour and compared the results with the ones obtained using scalp FECG. Time domain, frequency domain, non-linear Poincaré plots and indices at different lags were used to describe/analyse HRV.

It was shown that the use of the autocorrelation method to extract the beat-to-beat intervals of heart rate from Doppler envelope signals is an accurate approach, whereas we could not obtain the same quality of results using either the Wavelet Transform or the Hilbert-Huang Transform as standalone methods.

Our findings indicate that beat-to-beat intervals of heart rate and HRV metrics extracted from Doppler ultrasound have a very good agreement with the ones extracted from the scalp FECG, providing the possibility of assessing fetal heart rate variations by external monitoring during pregnancy and labour when scalp FECG is not available.

Chapter 6

Analysis of FHR patterns during labour

"life is too short to be little" Benjamin Disraeli

6.1 Introduction.

In this chapter we describe the study made to identify FHR patterns of prolonged decelerations, through the use of the CTG analysis performed to data collected during labour and delivery. We present an option to model and quantify the ascending phase of decelerations, the recovery time of FHR, that may reflect the resilience of the fetus (Gibb and Arulkumaran, 1997). Finally we comment about the obtained results.

6.2 Data Collection/CTG extraction and segmentation.

Using the fetal heart rate determined as described in chapter 5 we extracted the uterine contraction trace from the files collected from the HP8040A monitor described in the previous chapter. We analysed the data set of 4 subjects, each one with 50 minutes of recording. We plotted both FHR and uterine contractions in the same trend of a CTG and divided them in segments of 10 min for analysis (Arulkumaran and D'souza, 2009). Later on we fitted a base line corresponding to the mean value of the FHR excluding accelerations or decelerations (Murray, 2007). After this we looked forward to identify decelerations with basis in the characteristics described in this chapter. Once localized the deceleration of the FHR we identify the Nadir and recovery sections of the traces as illustrated in figure 6.1.

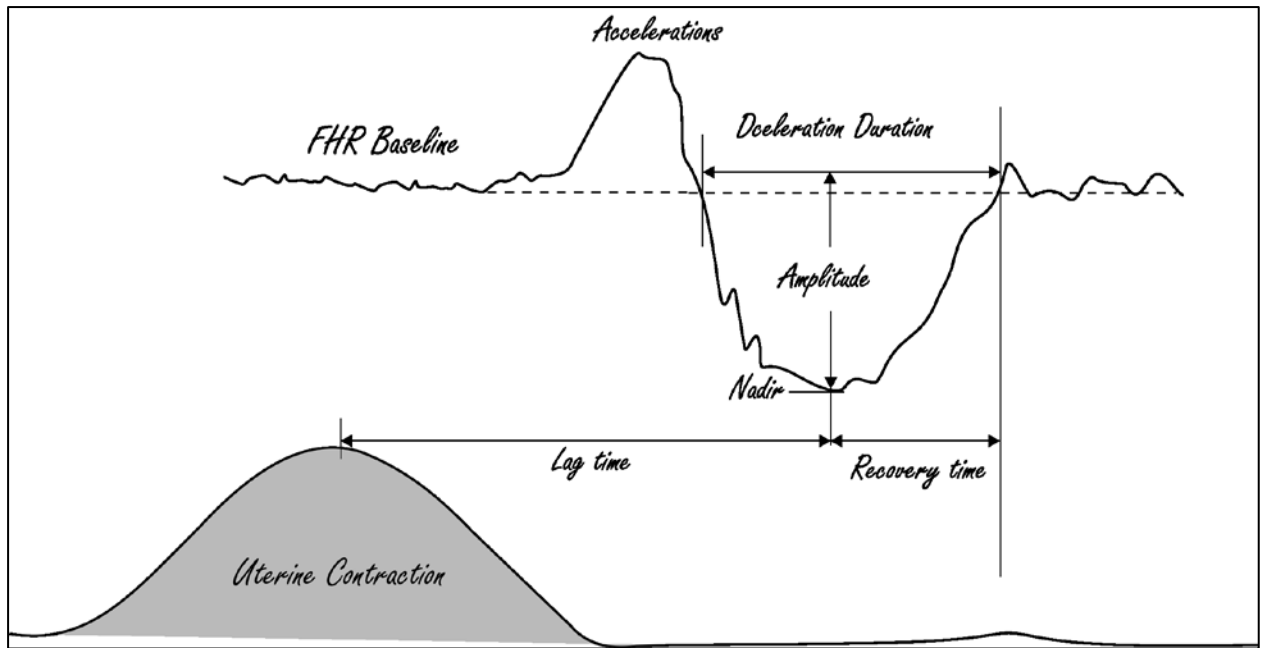


Figure 6. 1 Location of the recovery time, nadir and deceleration duration.

To measure the recovery time from the nadir of the deceleration to the baseline of fetal heart rate, an approach with basis in modelling the recovery by an exponential function was used. The approach used is described as follows: The trace during recovery time is modelled by

—

Where B =Base line, set up every 10 min, and the nadir of the decelerations is N =Lowest bpm. The amount of time analysed corresponding to the deceleration is given by V =Vector of time. The data collected presented a very normal and reactive FHR pattern without traces that might correspond to hypoxic decelerations. Nevertheless we performed the analysis at spontaneous decelerations, to study the behavior along time, and to verify if the frequency of spontaneous decelerations, will affect the recovery time to base line, indicating a “fatigue” of the defense/adaptive mechanisms of the fetus. This is shown in Figure 6.2.

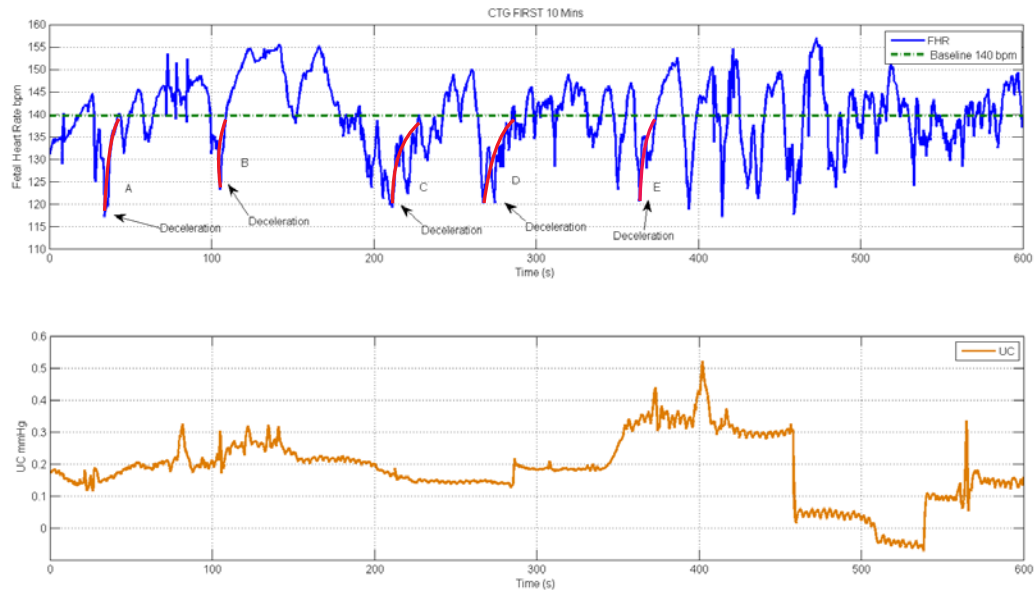


Figure 6. 2 The Green line is the baseline of FHR, red traces are the recovery path from the nadir of the deceleration, towards the baseline and the orange trace represents the uterine contractions.

The recovery time for the 5 identified decelerations, showed a fast and random behaviour, reflecting a good fetal oxygenation, unfortunately the frequency of the decelerations was not sufficient to monitor the trend of the recovery time vs. amount of spontaneous decelerations. From the rest of the CTG sections the identification of decelerations did not present a deep or duration to be classified beyond normal. (The rest of the CTG traces measured are included in Appendix A).

Table 6. 1 Deceleration recovery time.

Deceleration	Recovery time (sec)
A	2.77
B	1.71
C	11.57
D	12.66
E	2.69

6.3 Discussion.

From the analysis performed to the computed traces of CTG, there were no prolonged decelerations that could be consequence of a severe uterine contraction. The data sets presented the characteristics of well oxygenated fetuses. Only spontaneous and short decelerations were present. Nevertheless we argue that the approach presented here can be a valuable source of information in a larger CTG data base, since most of the research works related to the study of decelerations focus in the measurement of the lag time of the deceleration (Cao et al., 2006). Our approach presents a novel method to measure the possible “fatigue” of the fetus to overcome hypoxic scenarios and we strongly believe our approach will provide valuable information about the status of the fetus as the exponential model we used is intrinsically more robust than any detector of nadir and baseline.

Chapter 7

Summary and Conclusions

“The achievement of one goal should be the starting point of another” Alexander Graham Bell.

7.1 Summary

Complications of pregnancy, labour and delivery represent the main risk for perinatal asphyxia (Avery *et al.*, 1994.). Neonates asphyxiated at birth who develop hypoxic-ischaemic encephalopathy (HIE) have a very high risk of death (20-50%) and as many as 25% of the survivors show signs of cerebral palsy with major motor-cognitive impairment (Avery *et al.*, 1994., Robertson *et al.*, 1989, Vannucci, 1995). Early detection of signs of asphyxia can improve outcome by prompting appropriate medical intervention. Continuous direct assessment of fetal blood oxygenation levels is a puzzle not yet solved. The issue of identification of early signs of hypoxia that can evolve to chronic asphyxia has been addressed by a wide diversity of fetal monitoring methods that go from physical auscultation to the use of pH analysis from scalp blood samples, among others, nevertheless the antepartum period represents a closed frontier for some of these techniques and since it is not possible to have an experienced clinician or nurse at all times for each mother at labour, the use of electronic fetal monitoring has been extensively applied as an option for monitoring ‘at all times’, obtaining the FHR and monitoring fetal oxygenation indirectly.

Although through electronic fetal monitoring it is possible to achieve a high sensitivity to changes in the FHR and there has been a continuous fall in the incidence of HIE (Smith *et al.*, 2000), difficulties and inconsistencies in the interpretation of FHR patterns and lack of standardization contribute to the poor specificity of CTG and automatic monitoring in general (Murphy *et al.*, 1990, Nelson *et al.*, 1996, NICHD, 1997). As a result, a large number of false-positives are subject to unnecessary intervention, such as cesaerean delivery, thus

contributing to increased costs and risk of complications. Even among experimented clinicians the interpretation of the observed traces is very subjective.

Finding a robust method to identify and characterize asphyxia/hypoxia episodes from information contained in the fetal heart rate during labour and delivery (including the analysis of its variability) is still a challenge and there is a compelling need for a better system to monitor accurately the status of the fetus (Freeman et al., 2003) and avoid late or wrong interpretations of FHR traces that might result in injuries (Murray, 2007). To tackle this challenge, both linear and non-linear methods have been explored in this thesis to study HRV as a marker of asphyxia/hypoxia in two different physiological systems: 1) Animal model with different lengths of asphyxia 2) human fetus during labour and delivery.

7.2 Main findings of the study

In chapter 4 we presented the analysis of HRV as a marker of asphyxia (Cardona Rocha and Schlindwein, 2008) and studied its behaviour before and after asphyxia periods (Cardona and Schlindwein, 2009) using a novel optimal combination of some of the linear and non-linear methods proposed in chapter 3. The selection is optimal in the sense that it identified the most sensitive indices to characterize HRV variations before, during, and after different lengths of transient asphyxia episodes (1, 3, 5, and 7 min.). The individual characteristics of each of the techniques selected are complementary, and enable a more complete characterization of HRV, as often when linear methods (SDNN, STDH, RRMSDD) are not able to reflect variations, non-linear approaches (ApEn, SamEn, SD1, SD2, and $\alpha 2$) can.

In chapter 5 we investigated a comparison of three methods, autocorrelation function, Hilbert-Huang and Wavelet transforms, to extract beat-to-beat intervals of fetal heart rate from Doppler ultrasound, as a reliable option when the scalp FECG is not available or its use is not recommendable. From the comparison of the beat-to-beat intervals obtained from the

three proposed techniques, the autocorrelation function produced the most accurate results when compared with beat-to-beat intervals extracted from scalp FECG signal, which was used as the gold standard (Cardona and Schlindwein, 2010). Although the autocorrelation approach has been extensively used, to the best of our knowledge this is the first time such a detailed comparison was performed. Our findings indicate that the beat-to-beat time series obtained from the Doppler ultrasound was in agreement with the time series obtained from scalp FECG, hence it is suitable to perform HRV analysis from it. The study also used some of the linear and non-linear markers described in chapters 3 and 4. The obtained HRV values presented minimum differences, reflecting the suitability of the use of Doppler ultrasound to perform HRV analysis during labour and delivery (Cardona Rocha et al., 2011).

It has been described that a slow recovery from decelerations can represent a sign of fatigue of the defence mechanisms of the fetus to overcome hypoxic events (Murray, 2007). In chapter 6 we were able to model the shape of fetal decelerations and measure recovery times from the bottom of the decelerations to base line of FHR, but our data sets did not present marked decelerations and the amount of spontaneous decelerations measured did not have an impact on the behaviour of the recovery time, from where we were able to infer that the data sets used here corresponded to well oxygenated and healthy fetuses.

7.3 Conclusions

It is known that changes in the FHR during labour and delivery, specially a marked decrease in FHR known as ‘deceleration’, can be related with umbilical cord compression. These decelerations, depending of their magnitude and duration, can be the starting point of chronic hypoxia episodes. Timely detection and characterization of these episodes is crucial for a positive outcome for the fetus.

Direct determination of fetal oxygenation levels is complicated due its inaccessibility during the first stages of labour. HRV can be used as an indirect proxy for oxygenation levels, but scalp FECG cannot be used before ‘crowning’ and even then its use is not recommendable due to risk of infection. This situation was addressed in the course of this study through the use of Doppler ultrasound signals which were processed using autocorrelation function allowing accurate detections of beat-to-beat intervals. This was corroborated by comparison with RR intervals extracted from the scalp FECG as a gold standard. We suggest that by using a multiparametric HRV analysis and combining it with the tool to characterize the patterns of decelerations-recovery time, it would be possible to detect and quantify the degree of the injury due to asphyxia. This could improve the outcome during labour and delivery, where detection of asphyxia has been a long pursuit.

7.4 Future Work

The efforts towards reducing risks during delivery and improving the fetal quality of life will continue until mortality and morbidity due to antepartum and intrapartum complications caused by asphyxia/hypoxia are under control. The use of a selected set of methods and techniques to perform a more complete analysis of HRV is an advance and the techniques for characterizing HRV that we suggested and implemented in this work are a good starting point, but before they can be applied clinically it is necessary to collect more data and build a

large database, including different fetal pathological conditions. With such database it would be possible to study the sensitivity and specificity and measure the statistical significance of the obtained results.

Another avenue to explore is the implementation of a cot-side system to measure these parameters and exhibit them to medical / nursing staff in real-time. During our research we have considered the idea of using LabView to produce such a system to monitor HRV parameters along with FHR traces in real-time, we strongly believe that such implementation would be a great contribution to improve the fetal wellbeing.

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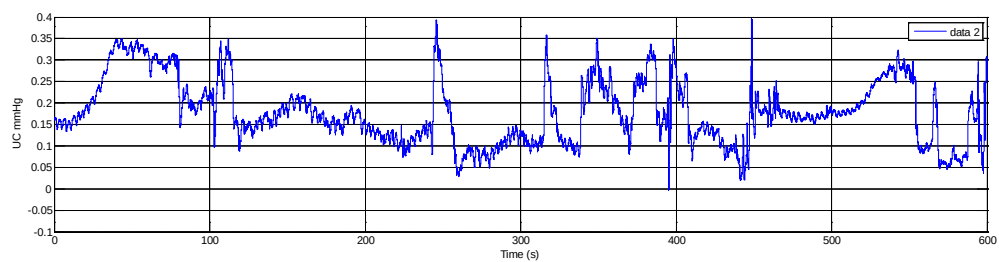
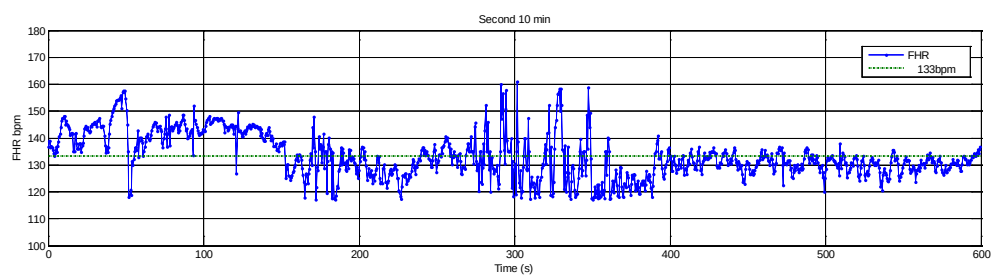
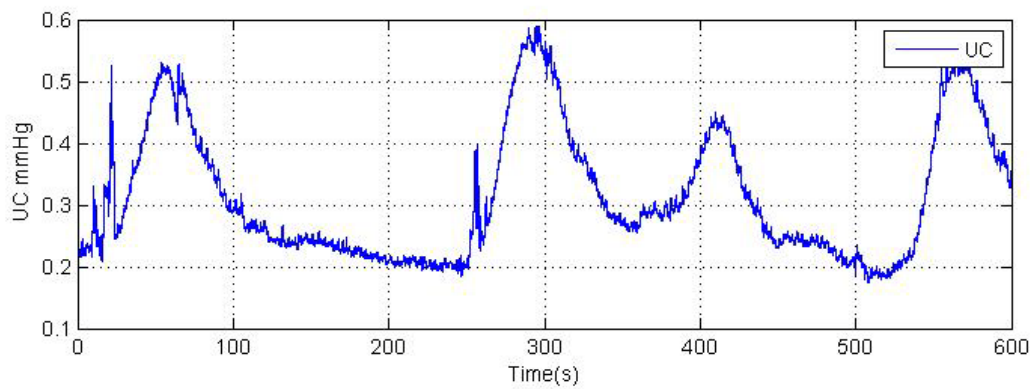
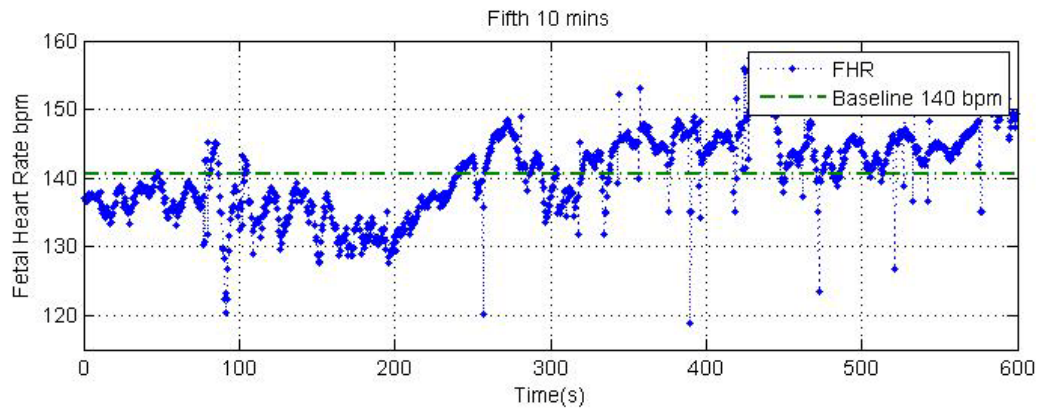
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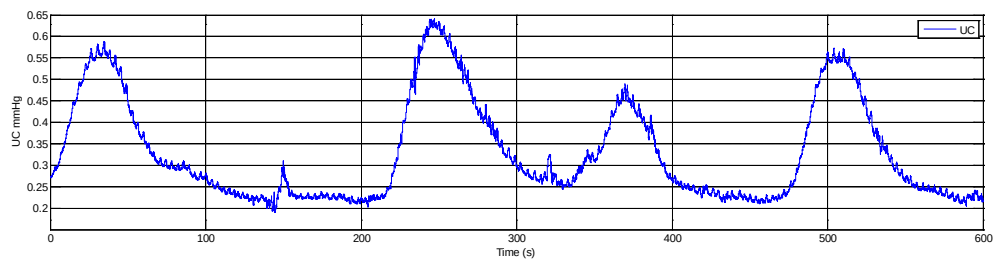
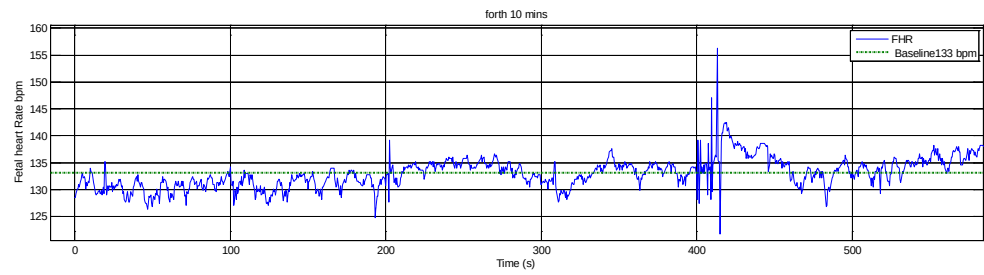
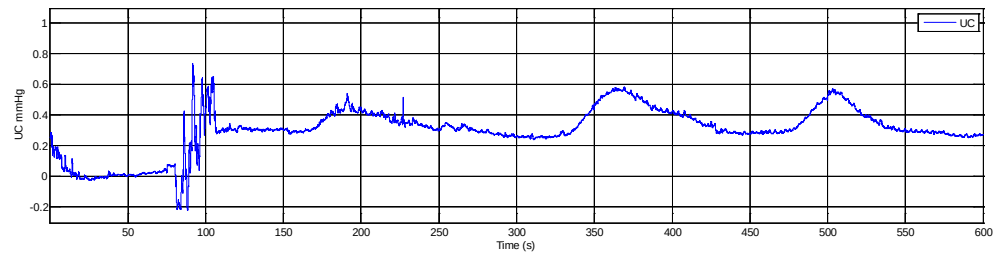
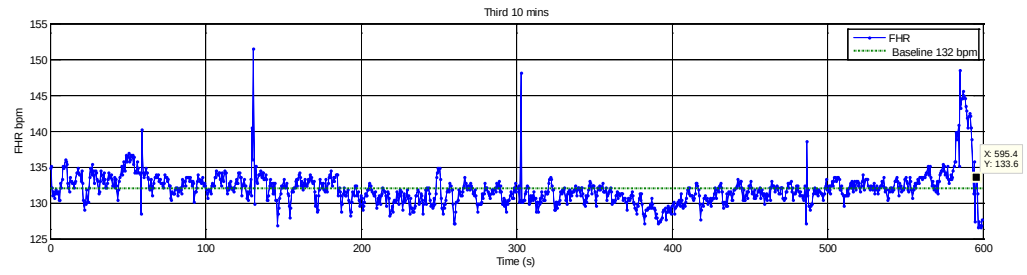
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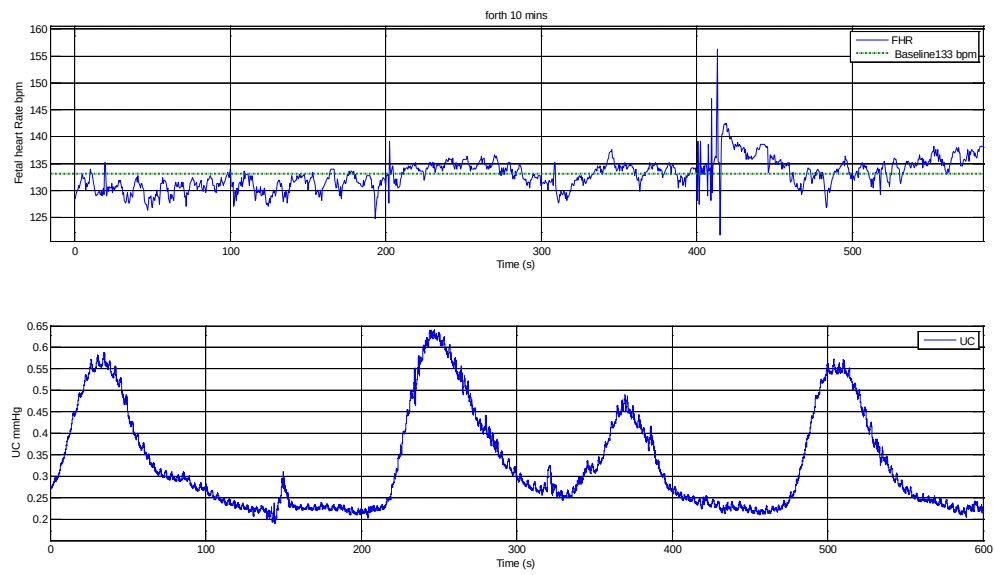
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Appendix A

Next are the traces that we obtained through our RR detections from the CTG from the data collected during labour and delivery.







From the constructed traces of CTG we were able to infer the good outcome during labour and delivery, the presence of regular contractions that didn't affect the fetal heart rate pattern is evidence of it.